The first is the requirement set forth in section 131 of the bill that certain information appear in all prescription drug advertisements. We are strongly opposed to this provision.

The second topic I will discuss is contained in sections 121–126, relating to the illicit distribution of barbiturate and stimulant drugs. With some qualifications, we favor this proposed legislation.

PRESCRIPTION DRUG ADVERTISEMENTS

Section 131 of H.R. 11581 would amend section 15 of the Federal Trade Commission Act. It would deem any prescription drug advertisement to be misleading, and thus in violation of law, unless it contains a conspicuous, full, and accurate statement of the efficacy of the drug, as well as a conspicuous and truthful disclosure of the drug's formula, side effects, and contraindications.

The PMA supports, unreservedly, the principle that no drug should be marketed without full disclosure of its actions and limitations. This principle was formally approved in May of 1958 by the PMA in the form of a statement of principles of ethical drug promotion. This is attached to my statement for insertion in the record of these proceedings.

Nevertheless, despite our support of the objectives of full disclosure, we are strongly opposed to section 131. It is wrong in principle to require, as this section purports to do, that every advertisement contain full disclosure of the drug's actions and limitations. Furthermore, it would be a practical impossibility for industry to comply with this provision.

Section 131 is based upon a fundamental misconception of the function of medical journal advertising. This misconception is that physicians commonly prescribe drugs on the basis of journal advertising alone, thus necessitating full disclosure with each ad. This simply is not the fact. Physicians do not prescribe drugs on such a basis.

The function of medical journal advertising is to attract the attention of the physician and to remind him of particular products. It seeks to remind or impress, to arouse curiosity, and to encourage further investigation. It seeks to alert him to established as well as new areas of use and benefit.

But journal advertising is not the basis on which a physician prescribes drugs for his patients. The physician is a learned, competent and licensed professional. He is an informed man. He is exposed, in addition to his years of training and professional experience, to a wealth of informational and educational material on each drug. This includes brochures of the manufacturer, giving complete information as to indications, effects, dosage, routes, methods, frequency and duration of administration, and all relevant hazards, contraindications, side effects and precautions.

In addition to the extensive efforts of the drug industry, he is informed by medical literature, by impartial reports of the medical profession, by colleagues, by numerous reference works, by hospital and medical society meetings, and by special postgraduate education.

For further elaboration of the many sources of information available to the physician, I refer the committee to a statement by Dr. Theodore G. Klumpp. It was filed on behalf of the PMA in September of 1961 in connection with another bill that is pending before this

committee, H.R. 6471. This bill is quite similar in purpose and language to section 131 of H.R. 11581. The objections raised by Dr. Klumpp apply equally to section 131 of the present bill. Accordingly, I am submitting Dr. Klumpp's statement and request that it be included in the record of these hearings.

The efforts of the American Medical Association especially warrant attention here. Dr. Blasingame, executive vice president of the AMA, described these efforts in a letter on H.R. 6471, dated August 10, 1961. This was directed to the Subcommittee on Health and Safety of this committee. This improved and extensive program for providing information to physicians in the field of drug therapy was described in exhibits to Dr. Blasingame's statement. Under this program the AMA will keep before all physicians complete and continuing data about new drugs and drug modifications.

The physician understands clearly the distinction between reminder advertising and the wide range of informational and educational materials which are available to him.

This distinction is also well understood by the Food and Drug Administration. As the members of this committee know, Congress has charged the FDA, through supervision of drug labeling, with seeing that adequate information is available to the medical profession. Thus, Congress has properly distinguished "advertising," which is subject to the jurisdiction of the Federal Trade Commission, from "labeling," which is regulated by the FDA. This distinction between advertising and labeling was soundly conceived and should be maintained.

In the FDA regulations on the labeling of prescription drugs, full disclosure is not required in so-called "reminder piece labeling." Furthermore, the FDA regulations do not require full disclosure in the package insert when drug directions, hazards, warnings, and use are commonly known to licensed medical practitioners. I mention these "labeling" regulations in order to point out that the concept of reminding the physician, which is recognized in these regulations, shoulld be even clearer in advertising than in labeling.

To explain the essential difference between typical reminder advertising and informational material, I should like to show this committee examples of both journal advertisements and informational brochures.

I have examples of recent Abbott medical journal ads. Obviously, they make no attempt to tell everything about the product. If I may, Mr. Chairman, I call your attention particularly to the nembutal ad. You can see what I mean by our definition of purely reminder advertising. These types of ads alert, remind, call attention to some but not all aspects of the drug. But I might say that these ads, like our printed material, were subjected to medical scrutiny. The responsibility for approval of all ads is vested in our chief medical officer who is a vice president of our company and a member of its board of directors.

I also have a display of Abbott booklets which contain some 800 pages of meticulously prepared reference material. These documents, and not the advertisements, contain the full information for prescribing our drugs.

I remember this afternoon, Mr. Chairman, that you asked the question as to what drug companies do to supply the practicing physi-

cian with contraindications, dangers, warnings and so forth. These are the types of full disclosure brochures that are made generally available through the industry by all companies to physicians, and you will note if you glance through them that they contain reference to contraindications, side effects, warnings, so forth and so on.

I would like to emphasize, too, that some of these booklets go far beyond giving facts solely about our products and supply basic information about specific areas of medicine. A few of these are "Use of Blood, Fluids and Electrolytes"; "Parenteral Administration"; "The Vitamins"; and "Symptoms and Treatment of Overdosage with Selected Abbott Products." An unusual one is "Symptoms and Treatment of Overdosage with Selected Abbott Products." This is used in teaching institutions. Booklets such as these are widely used in teaching programs at medical schools and hospitals. They are furnished freely, without charge, incidentally.

These examples were selected from those sent out by Abbott Laboratories. Of course, materials comparable to these are prepared by other drug manufacturers for their own products and areas of special interest.

Such materials illustrate the pains to which we go to make sure that the practitioner has all of the information he needs. They show the concern of the manufacturer who wants above all to make certain that his product is used correctly. He wants to be certain that maximum benefit is obtained from the drug. In this way he best assures his own success.

To further show the basic distinction between the journal advertisement and the total library of information available to the physician, I refer the committee to a letter which Abbott Laboratories submitted on H.R. 6471 on November 14, 1961. As I have said, section 131 of H.R. 11581 is quite similar to that bill and the comments in our letter are pertinent here. In our letter we referred to a statement that the Federal Trade Commission filed with this committee in September 1961. In that statement a reminder advertisement for one of our prescription drugs, Oretic, was listed as an example of the failure to give space to a discussion of side effects and contraindications. The FTC asserted that " * * * only the pharmacist ordinarily would have the opportunity of seeing the manufacturers' printed warning of side effects and contraindications for his products that appear on the package inserts."

The FTC statement apparently rests on the erroneous assumption that the advertisement was the only information which the physician saw. Actually, Abbott had already supplied to the medical profession exhaustive information about Oretic, including complete detail on dosages, precautions and side effects.

The advertisement cited appeared in the October 22, 1960, issue of the Journal of the American Medical Association 14 months after the product was introduced. The advertisement called attention to this drug for use in edema and hypertension. With this reminder, the physician could and would refer to detailed data which he had in hand.

What was the scope of this information? At the time we first marketed Oretic in 1959, we began distributing a 16-page physician's reference booklet containing complete information about the drug.

Abbott distributed more than 120,000 copies of this booklet. Our first medical journal presentation of Oretic, also in the *Journal of the American Medical Association* was an eight-page insert containing complete statements on precautions and side effects. Later, this eight-page insert was also mailed directly to 106,000 physicians.

In these and other ways, the marketing of Oretic was fully consistent with the principle of full disclosure. Furthermore, information about this drug was available to the medical profession from a variety of sources other than Abbott Laboratories, as also shown in our letter to this committee, which is attached to this statement.

It should be obvious that physicians do not, are not, and should not be expected to prescribe on the basis of reminder advertising.

To require medical journal ads to carry the information called for by section 131 would not add to the information physicians receive about drugs. Instead section 131 would eliminate reminder-type advertising, which serves a useful and legitimate function for the medical profession and for the drug industry.

Section 131 would also present extremely troublesome practical problems for drug manufacturers. It is mechanically, as well as medically, impossible to include in single-page or smaller advertising space complete data bearing on efficacy, contraindications and side effects. So-called full disclosure under section 131 gives only the appearance of completeness. Actually, it isn't complete within the meaning of medical practice.

Our medical schools insist that prescribing be done on the basis of facts—all the known facts. As professionals, physicians expect to be thoroughly familiar with the drugs they are prescribing. They expect to know more—much more—than could possibly be included in a journal ad, even if it contained the data required in section 131.

If we abbreviate basic facts in journal advertisements, it might well encourage physicians to prescribe without going to the complete literature. This would lessen their professional knowledge about drugs rather than increase it.

Few medical journal advertisements could contain a full or accurate statement covering every possible reaction or effect, especially with complex drugs constantly undergoing evaluation. If some selection is to be made, who is to judge what portions of the full library available to the physician should be included? How could one satisfy the varying needs of the practicing physician? One warning in an ad might be of no concern to one practitioner, yet vital to another.

In addition, there is always a variety of scientific opinion about the effectiveness of any drug. In many cases it is necessary to set forth the findings and conclusions of a great many researchers so that individual practitioners may draw their own conclusions. So we come down to the fact that the use of a drug depends on the judgment of the physician and the medical history of the patient. Each patient is separate and unique, to be treated according to medical judgment.

The ultimate question, then, is this: Would section 131 help the physician in treating patients? We believe it would hinder rather than aid the further progress we all seek in the field of health care. For journal advertising was never intended to provide, and as a practical matter cannot provide, the total data which the physician should have available as a basis for prescribing for his patients.

The plain fact is that this data is now readily available to the physician, and he makes good use of it.

It should be noted that the proposed requirements could have a most harmful effect on medical journals. They depend on pharmaceutical advertising as their principal source of income. Medical journals serve as a useful educational aid for both the specialist and the general practitioner. Most likely, many worthwhile journals would be forced to curtail medical articles and even to cease publication. Thus a valuable source of medical knowledge would be lost to the profession.

In concluding my comments on section 131, I should like to refer the committee once again to Dr. Klumpp's statement on H.R. 6471. As suggested there, if it is believed that some additional safeguard is necessary, the PMA proposes that all advertisements of prescription drugs bear the following statement:

Before prescribing, be sure to consult the manufacturer's literature for information about possible side effects and contraindications.

BARBITURATES AND STIMULANTS

Sections 121 through 126 of H.R. 11581 provide for special controls intended to reduce the illicit distribution of barbiturate and stimulant drugs.

These drugs are highly beneficial and have many important uses. When prescribed under medical supervision, they are effective and safe. They have long been drugs of choice for a variety of medical indications. At present they can be dispensed only on prescription of a licensed practitioner.

According to the testimony of former HEW Secretary Ribicoff, abusive, nonmedical use of certain of these drugs presents serious public health problems, for this illicit use in quantities far exceeding the usual dose may lead to abnormal and antisocial behavior.

The PMA therefore supports amendments strengthening Federal power to prevent such illicit distribution. But, because of the extraordinary nature of the proposed legislation, the PMA believes that any action should be carefully limited to proven needs. Unneeded authority should not be granted, nor should unwarranted burdens be imposed.

We favor provisions that would (1) require manufacturers of barbiturates and stimulates such as the amphetamines to register with FDA; (2) require manufacturers to keep adequate records; and (3) limit and specify the classes of persons who may deal in these drugs. We also agree with the position taken by the administration that the Federal Government, if it is to control this illegal traffic, must have the power to reach intrastate as well as interstate commerce.

We are commenting on these provisions because they are included in H.R. 11581. It should be pointed out, however, that the control of amphetamines and barbiturates has been extensively studied in the House. Also, in the Senate, Senators Dodd and Wiley have cosponsored S. 1939, dealing with the control of illicit traffic in these drugs. It might therefore be desirable for this area to be treated in a separate bill.

We have a number of suggestions to offer. In order to conserve the time of this committee, I am attaching to my statement a memorandum setting forth our recommendations. I will only refer to two of them at this time.

First, the severe criminal sanctions should be applied only to illicit peddlers of these drugs, and not to the people they are victimizing.

The supporters of this legislation—both in Government and in industry—agree that this illicit trade can be stopped only by eliminating the peddler. FDA has publicly taken the position that it wishes to prosecute only the peddlers, and not their customers as well. As it stated in its answers to questions put by this committee—

*** * * it may well be that possession for personal use and not for disposition to others could be eliminated as an offense without greatly impairing the effectiveness of the law in actual practice.**

We believe the illegal possession clause presently contained in the bill is needlessly severe and of marginal, if any, value in controlling improper use of these drugs. It might encourage physicians to prescribe other, perhaps less effective, drugs even when a barbiturate or amphetamine would otherwise be the drug of choice. For these reasons, we are opposed to any measure that would go so far as to subject otherwise innocent individuals to Federal criminal law.

Second, this legislation, which grants extraordinary powers to the FDA, should be clearly limited to those drugs for which there is evidence of significant misuse and abuse; namely, barbituates, amphetamines, and certain derivitives of phenethylamine. The definitions in H.R. 11581 should make the limitation to these drugs clear.

In conclusion, I wish to reemphasize that the PMA is in favor of measures to combat illicit peddling and use of barbiturates and amphetamines. Any such measures, however, must not interfere with the important place these drugs have in many areas of medicine.

The CHAIRMAN. I believe, Mr. Cain, you said you were filing or would file with the committee a memorandum setting forth recommendations.

Mr. CAIN. Yes, sir.

The CHAIRMAN. Do you have that memorandum?

Mr. CAIN. I think it should be attached to the file that was submitted to you, sir. It is dated August 20, 1962. It is on the bottom of the file I think.

The CHAIRMAN. Yes, here it is. I observe that you have a good many attachments to your statement. Of course the one with reference to yourself will be included at the appropriate place. Now, as to the statement of principles of ethical drug promotion, which you referred to in your statement, you would want that included in the record would you not?

Mr. CAIN. Please, sir.

(The information mentioned follows:)

MEMORANDUM ATTACHMENT TO STATEMENT OF GEORGE R. CAIN

AMENDMENTS TO SECTIONS 121–126 OF H.R. 11581, RELATING TO BARBITURATES AND STIMULANT DRUGS, RECOMMENDED BY THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION

I

In order to implement our recommendations that the innocent victims of the illicit traffic in barbiturates and stimulant drugs not be caught up in the pervasive criminal provisions of the bill, the words "sell, or possess for sale," should be added after "process" in section 509(f), on page 22, line 15. Consistent with this, subsections (c) and (d) of section 509, on pages 24 and 25, should be deleted, and the succeeding subsections properly renumbered. In addition, section 123, on page 27, lines 19–23, should be amended so as to read, "(o)(1) The manufacture, compounding, processing, sale, or possession for sale of a drug in violation of section 509(b); (2)(A) the failure to prepare or obtain, or the * * *."

II

This legislation, which grants extraordinary powers to FDA, should be clearly limited to those drugs for which there is evidence of significant misuse or abuse. The evidence of misuse, and thus of need for greater public protection, relates only to barbituates, amphetamines, and certain derivatives of phenethylamine. We believe that the extension of this legislation beyond these drugs is wholly unwarranted, and that the definitions in H.R. 11581 should make this limitation clear and unambiguous.

The definitions, as presently drafted, would permit the Secretary to bring within the proposed legislation any substance which the Secretary finds to be habit forming because of its stimulant effect on the central nervous system. The use of the term "habit forming" is inappropriate. The purpose of these extraordinary controls is to eliminate the misuse of certain drugs which because of their stimulating effect on the central nervous system, rather than any habituating properties, pose a threat to public health and safety. There has been no showing that any other possibly habituating drugs pose a similar threat of antisocial behavior due to their abusive nonmedical use. Therefore, there is no need for all such drugs being placed within the confining conditions of this bill.

The Food and Drug Administration itself, in its answers to questions posed by Congressman Williams, recognized that the problem of antisocial behavior was presently limited to barbiturates and stimulant drugs such as amphetamine. If in the future, other drugs are shown to present social dangers, the PMA would, of course, support legislation strictly controlling their distribution. Until such time, however, we do not believe these controls should be extended beyond the area of proven need.

For this reason, we recommend that the committee adopt the definitions set forth below in place of those presently contained in proposed section 509(a)(1) and (2), pages 21–22 of the bill. We further recommend that each definition exempt products which contain other drugs in combination with such minor quantities of amphetamines or barbiturates that the product does not raise the possibility of illicit traffic. This concept, covering some over-the-counter products, is already well recognized by the FDA. The language we recommend is:

"(1) The term 'barbiturate' means any drug which contains any quantity of (A) barbituric acid or any of the salts of barbituric acid; or (B) any derivative of barbituric acid, which derivative has been designated by the Secretary under section 502(d) as habit forming; provided that such terms shall not include drugs containing in addition to any such barbiturate, a sufficient quantity or proportion of another drug or drugs to prevent the ingestion of a sufficient amount of barbiturate to cause a hypnotic or somnifacient effect; and shall not include any drug permitted to be sold over the counter without prescription;

"(2) The term 'amphetamine' means (A) amphetamine or any of its optical isomers; or (B) any salt of amphetamine, or any salt of an optical isomer of amphetamine; provided that such terms shall not include drugs containing, in addition to any such amphetamine, a sufficient quantity or proportion of another drug or drugs to prevent the ingestion of a sufficient amount of amphetamine to cause a stimulating effect on the central nervous system; and shall not include any drug permitted to be sold over the counter without prescription;

"(3) The term 'stimulant drug' means any derivative of phenethylamine which the Secretary, after investigation, has found to have become a threat to the public health and safety when used illicitly, because of its stimulant effect on the central nervous system, and by regulation has designated as a 'stimulant drug'; provided that any such regulation shall exempt from the provisions of this section any drug containing, in addition to such stimulant drug, a sufficient quantity or proportion of another drug or drugs to prevent the ingestion of a sufficient amount of such stimulant drug to cause a stimulating effect on the central nervous system."

III

As we have pointed out, the term "habit forming" is inappropriately used in this bill to refer to stimulant drugs. "Habit forming" is often taken to mean that the failure to use the drugs leads to physically debilitating symptoms—withdrawal symptoms or the so-called abstinence syndrome—and a craving is developed for the drug. This condition (properly characterized as "addiction") does not result from the use of stimulant drugs, according to Dr. Chauncey Leake, in his book, "The Amphetamines."

Moreover, the danger presented by these drugs, as detailed in testimony before the Senate and this committee, is not that they may be "habituating" (a term characterizing drugs taken regularly which do not produce cravings or withdrawal symptoms), but that taking them may so stimulate the central nervous system as to lead to antisocial behavior. Thus their habituating qualities are irrelevant to the threat they present, for withdrawal of the drug will remove the threat without presenting the danger of antisocial action due to cravings or withdrawal symptoms associated with addiction.

Therefore, line 23 on page 21 should be amended to read: "Barbiturates and Stimulant Drugs." Similar amendments should be made on line 25, page 20; line 15, page 22; line 25, page 23; lines 3–4, page 24; lines 9, 15, and 21, page 25; lines 7 and 17, page 26; line 10, page 27; and line 9, page 28.

IV

The PMA also recommends that the power to designate drugs should be qualified by the hearing and review provisions of the Federal Food, Drug and Cosmetic Act. This safeguard is consonant with the extraordinary controls placed on those who manufacture the drugs which these provisions would regulate. Therefore, a new section should be added to this portion of H.R. 11581, amending section 701(e) of the Food, Drug and Cosmetic Act by adding section 509 as one of the sections subject to the provisions of section 701(e).

V

While the PMA agrees that recordkeeping requirements must be complete and effective, we also believe that they should not be needlessly burdensome. For example, we see no reason for requiring each local druggist to record the address of the person to whom a drug controlled by section 509 is dispensed so long as the prescription presented shows the name and address of a licensed practitioner. We therefore recommend that line 3, page 26 (section 509(e)(1)) be amended to read:

disposed of, and the date of such transaction: *Provided*, That no record need be made of the address of any person to whom such drug is sold, delivered or otherwise disposed of if such sale, delivery or other disposition shall have been pursuant to a prescription showing the name and address of a practitioner licensed by law to prescribe barbiturates and stimulant drugs: *And provided further*, That there shall be no set form or forms for the foregoing records so long as they contain the required information.

VI

Finally, we suggest the deletion of section 125 of H.R. 11581, page 28, lines 16–21. This section permits the continued effectiveness of State laws.

This legislation, to halt effectively the illicit traffic in these drugs, must extend to all commerce, intrastate as well as interstate. The congressional findings properly call for such coverage. Section 125 might, however, encourage State legislation which will only increase the complexity of regulation without providing any additional significant public benefit. The PMA believes, moreover, that the field of barbiturate-amphetamine-phenethylamine regulation is one primarily and predominently of Federal concern.

Therefore, we recommend the deletion of section 125 so that the courts may, as specialized Federal controls evolve in practice, make appropriate determinations on issues involving conflicts between Federal and State law.

GEORGE R. CAIN

George R. Cain has been associated with Abbott Laboratories since 1940 and has been a director since 1947. He was elected president in 1958 and became board chairman and president in April 1962.

Mr. Cain was born September 9, 1910, in Noblesville, Ind. He attended Williams College from which he received his A.B. degree in 1933.

After graduation he joined the Equitable Life Assurance Society of the United States as a group department representative. In 1937 he became a general insurance broker with W. A. Alexander & Co.

Mr. Cain joined the Abbott sales department in 1940 as a member of the hospital division. In 1947 he was elected to the board of directors and was named secretary of the executive committee and administrative assistant to the president. He became a member of the executive committee in 1949, executive vice president and chairman of the executive committee in 1950, president in 1958 and chairman of the board and president in 1962. Mr. Cain is also a director of Abbott Universal, Ltd., and Abbott Laboratories, Ltd. (Canada).

He is a director of Evanston Hospital, a trustee of Northwestern University, a director of the Pharmaceutical Manufacturers Association, a director of International Harvester Co., and past chairman of the board of the Health Information Foundation.

Mr. Cain and his wife, Jane, reside at 115 Meadow Lane, Winnetka, Ill.

The CHAIRMAN. Do you intend for Dr. Klumpp's statement to be inserted in the record here too?

Mr. CAIN. I think it is already in the record, sir, since he filed it with your committee under the date of September 21, 1961, in which he commented on H.R. 6471, but for convenience——

The CHAIRMAN. You said we had it in that record?

Mr. CAIN. Yes, sir.

The CHAIRMAN. We could make it part of this record by reference.

Mr. CAIN. Yes, sir. It might be convenient only as a reference.

(See p. 325 for Dr. Klumpp's statement on H.R. 6471.)

The CHAIRMAN. Yes. And then you have a letter referred to of November 14, 1961, on the same subject. That is in the record and may be referred to by reference here.

Mr. CAIN. Yes, sir.

(See p. 331 for the letter dated Nov. 14, 1961.)

The CHAIRMAN. You had this exhibit A, "Physician's Reference on Oretic." I think we will receive that along with these other booklets that you presented for the record.

Mr. CAIN. Thank you very much, sir.

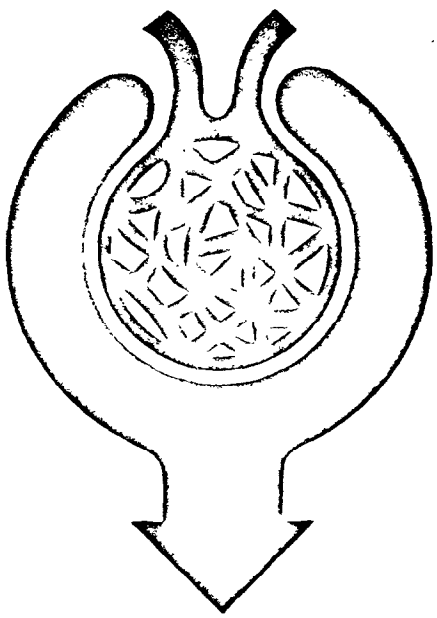
The document referred to follows:)

EXHIBIT A

PHYSICIAN'S REFERENCE

ORETIC™

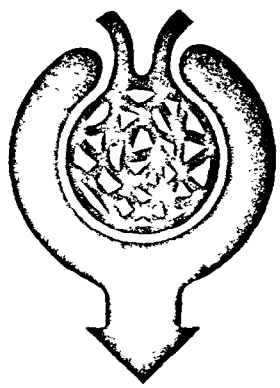
(HYDROCHLOROTHIAZIDE, ABBOTT)



YOUR MOST POTENT MEANS
WHEN THE END IS DIURESIS

ABBOTT LABORATORIES • NORTH CHICAGO, ILL.
RADIOPHARMACEUTICAL LABORATORIES
OAK RIDGE TENN

279



ORETIC the most potent
and effective oral
diuretic-antihypertensive
yet discovered.

ORETIC high therapeutic ratio
and low toxicity
—effective doses
only 1/10 to 1/15 those needed
with chlorothiazide.

ORETIC for renal, cardiac,
steroid edema and edema
and toxemia of pregnancy.

ORETIC alone, effective
in mild hypertension;
with other agents,
effective in moderate to
severe cases.

ORETIC useful in
management of
obesity and
premenstrual tension.

ORETIC | YOUR MOST
POTENT MEANS
WHEN THE END
IS DIURESIS.

ORETIC | CONTENTS

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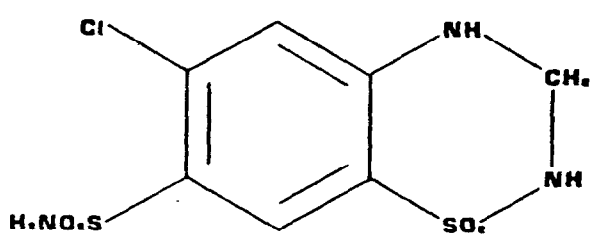
ORETIC

is the Abbott trademark for hydrochlorothiazide, a synthetic heterocyclic compound possessing diuretic properties. This agent enhances the excretion of sodium and chloride by a direct action on the renal tubules similar to that of the mercurial diuretics. It also inhibits the action of carbonic anhydrase. It is as effective as chlorothiazide, but at considerably reduced dosage (from one-seventh to one-twentieth of the dose of the parent compound).

ORETIC is a white, crystalline solid, which is slightly soluble in cold water or alcohol, and more readily soluble in alkaline solutions. Chemically, it is 6-chloro-3,4-dihydro-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide, and has the following structural formula:



ORETIC—TRADEMARK FOR HYDROCHLOROTHIAZIDE, ABBOTT

ORETIC | METABOLIC EFFECTS

The primary action of ORETIC appears to be on the renal tubules, where the reabsorption of both sodium and chloride are blocked to approximately the same degree. This results in a profound increase in the excretion of these electrolytes. There is also a much smaller increase in the excretion of potassium and bicarbonate.

Particularly when fluid has been retained in the body, the excretion of these electrolytes causes a secondary excretion of water. The action resembles that of parenterally administered mercurial diuretics.

Although the action of oral and mercurial diuretics on the renal tubules has been the subject of a number of studies, a full explanation of the mechanism has not yet been offered. However, current studies show that renal blood flow and glomerular filtration rate remain essentially unchanged.

The action of ORETIC in lowering elevated blood pressure is also not fully understood. After working with the heterocyclic diuretics (chlorothiazide and hydrochlorothiazide), a number of investigators have offered theories regarding their mode of action.

Freis, et al.,[1,2] and Tapia, et al.,[3] have drawn attention to the alteration in plasma volume which may be observed for long periods of time in patients receiving maintenance therapy with chlorothiazide. They suggest that this may alter the fundamental reactivity of the arterioles to other drugs, and they have shown that the fluid changes approximate those seen in patients receiving the rice diet, or on very restricted sodium intake. It is also well known that patients on rigid sodium restriction respond better to the usual antihypertensive drugs.

Wilkins and his associates[4,5] believe that the redistribution of fluid and electrolytes are important factors in the antihypertensive effect of oral diuretics of this class. However, these authors also suggest that agents of this type may have an antihypertensive action not specifically related to the diuretic effect.

ORETIC | INDICATIONS

There are two primary indications for use of ORETIC—elimination of excess fluid (edema from any cause) and treatment of hypertension. ORETIC may be used alone in mild cases of hypertension or in combination with other antihypertensive agents in management of more severe cases.

RENAL EDEMA ORETIC is of value in the management of nephrotic edema caused by various forms of renal disease. Its employment may reduce the necessity for very rigid sodium restriction usually required when ACTH or steroids are administered. However, severe renal impairment may render kidneys unresponsive to any form of diuretic therapy. If a response is not obtained, and if clinical and laboratory studies indicate progressive renal failure, therapy with ORETIC should be discontinued.

CARDIAC EDEMA In congestive heart failure, ORETIC produces a copious diuresis comparable to that produced by parenterally administered mercurials. The potency, long-term effectiveness and safety of ORETIC make it an agent of choice for maintenance therapy in cases of cardiac failure. Symptoms such as dyspnea, orthopnea and chronic cough may be dramatically improved. ORETIC may reduce the necessity for salt restriction, and is thus particularly useful in patients who find it difficult to follow a salt-free diet.

If desired, ORETIC may be used together with mercurial diuretics, though this is seldom necessary. It should be remembered that successful employment of diuretic agents does not eliminate routine measures in the treatment of heart disease such as rest, digitalization and careful attention to the diet.

TOXEMIA OF PREGNANCY ORETIC is especially useful when salt and fluid retention present a problem. It should be used as an adjunct to the usual measures and, if necessary, may be combined with the use of more potent antihypertensive drugs. The dosage of these is generally reduced when

ORETIC is employed and the danger of toxic side effects is thereby minimized.

PREMENSTRUAL TENSION, EDEMA IN PREGNANCY Small doses of ORETIC are often useful in overcoming the antidiuretic effect which may be seen, in some patients, in the above conditions.

STEROID EDEMA The administration of adrenal and pituitary hormones (ACTH, cortisone, hydrocortisone, etc.) may be accompanied by salt or water retention leading to clinical edema. ORETIC may be successfully employed for the treatment of these secondary effects and may eliminate the need for cessation of steroid therapy.

HYPERTENSION ORETIC is indicated in the management of the majority of cases of hypertension. In mild cases, it can be used alone and will often eliminate the necessity for a rigidly controlled salt-free diet. In more severe cases, it may be employed in conjunction with any of the standard antihypertensive drugs including Harmonyl®, and other rauwolfia derivatives, hydralazine, veratrum alkaloids and ganglionic blocking agents. It may also be of value, and produce improved control of blood pressure, in patients who have received a surgical sympathectomy.

ORETIC | DOSAGE AND ADMINISTRATION

The adult dosage of ORETIC is in the range of 25 to 200 mg. daily. Usually 75 to 100 mg. will produce the desired effect.

This may be given as a single dose in the morning, or if desired (particularly with larger doses) the tablets may be administered two or three times each day. Laboratory and clinical evidence indicates that ORETIC is as effective as chlorothiazide, but that the equivalent dosage is only one-seventh to one-twentieth of the amount required with the latter agent.

CONTROL OF EDEMA ORETIC is the most potent and most effective oral diuretic agent available. It will usually eliminate the necessity for paren-

teral administration of mercurials and will often permit a reduction in rigid sodium restriction. It may be given alone or in combination with other agents for the elimination of retained fluid.

Dosage should be adjusted in accordance with the patient's response. At the start of treatment, 50 to 100 mg. may be administered after breakfast. If necessary, this dosage may be repeated later in the day, and be administered twice daily for several days until the patient's weight approaches its non-edematous value.

When control of edema has been established, it may be maintained by daily or intermittent therapy with small doses. In some patients, a daily dose as low as 25 mg. may be effective; in others, as much as 150 mg. may be required.

When regular therapy is employed, it is important to keep a careful and constant watch on electrolyte balance. Particular care should be taken to guard against potassium depletion. Patients on regular maintenance therapy should be instructed to take approximately 8 ounces of tomato, orange or citrus fruit juice two to four times *each day*. If this is not possible, potassium chloride may be administered by mouth at a dosage of 1 gram two to four times daily.

In many patients, intermittent therapy is all that is necessary to maintain control of edema. Thus, administration of ORETIC may be reduced to every second day or to three or four consecutive days in each week. The optimum dosage and time interval between administrations can only be determined by individual trial in each patient. Intermittent therapy is recommended (when adequate), since this will reduce the possibility of producing electrolyte imbalance.

It is important to realize that the elimination of edema fluid does not necessarily cure the underlying disease or condition which initially caused the retention of the fluid. An appropriate treatment which takes into consideration the underlying cause of the edema should not be neglected.

MANAGEMENT OF HYPERTENSION At the start of treatment it is best to administer ORETIC early in the day. For the first few days, some diuretic action may be apparent, and it is more convenient for the patient if this occurs during the waking hours. When fluid balance has adjusted, the diuretic action is not usually noticeable. Therefore, at the start of treatment it is recommended that the total daily dose should be given after breakfast. For maintenance therapy, the daily dose can be divided and given two or three times a day. Dosage must always be individualized, but the following suggestions should provide guidance in establishing optimum benefit.

(a) **ORETIC** *used alone*

In mild cases of hypertension, a satisfactory response may be obtained without the use of potent antihypertensive agents. For initiating therapy, the average daily dose in the adult is 75 mg. After a few days, the dosage should be adjusted upwards or downwards, according to the response.

In general, the maintenance dosage should be the minimum which will produce the desired effect on blood pressure. A maximum dose for maintenance is generally considered to be about 150 mg. daily (which may be divided and administered as 50 mg. t.i.d.).

If the blood pressure does not respond to ORETIC alone, therapy may be continued while other more potent agents are added to the regimen.

(b) **ORETIC** *with Harmonyl or other rauwolfia derivatives.*

ORETIC may be administered to patients receiving rauwolfia alkaloids without an initial alteration in the dosage of these compounds. After a few weeks, the dosage of both agents may be reduced slowly, until the minimum amount necessary to produce the desired benefit is established.

Adjustments in dosage should not be made too quickly, since the

action of rauwolfia derivatives is prolonged. Thus, the effect of a reduction in dosage may not become apparent for some weeks.

If the desired benefit has not been obtained, Harmonyl may be added to the regimen of the patient receiving ORETIC alone. Therapy with Harmonyl may be started at a daily dosage of 0.25 to 0.5 mg. (one or two tablets). The dosage may be revised according to the individual response. The combination of ORETIC with Harmonyl will often prove effective in lowering the blood pressure in patients who do not respond satisfactorily to either agent used alone.

(c) **ORETIC** *with other antihypertensive drugs*

It must be remembered that regular administration of ORETIC tends to make the patient more sensitive to the action of other antihypertensive agents. Therefore, if drugs such as hydralazine or ganglionic blocking agents are employed, the initial dosage of these agents should be relatively small (approximately one-half of the recommended dosage when these agents are used alone). A satisfactory maintenance dose of the two agents can be established only by individual trial. Generally speaking, the maintenance dose of the additional agent will be less when it is employed with ORETIC than when given alone.

MANAGEMENT OF OBESITY In some obese patients, fluid retention is a complicating factor. In these cases, ORETIC may be helpful in promoting early weight loss. An average dosage is 25 mg. once or twice daily during the first few weeks of treatment.

The administration of a diuretic agent is *not* a substitute for dietary restriction, and the usual measures to limit the intake of total calories must be observed.

ORETIC | HOW SUPPLIED

ORETIC tablets are supplied in bottles of 100 and 1,000 in dosage sizes of 25 mg. (List No. 6978) and 50 mg. (List No. 6985).

ORETIC | **PRECAUTIONS AND SIDE EFFECTS**

Since ORETIC is the most potent and effective oral diuretic available, it is to be expected that small doses will markedly increase the excretion of fluid and electrolytes. Therefore, the dosage and frequency of administration must be carefully adjusted to the needs of each patient. All patients should be observed closely for early signs of fluid or electrolyte imbalance. Precautions against potassium depletion are described on page 6.

Early indications of electrolyte imbalance may include symptoms such as thirst, dryness of the mouth, lethargy, weakness and drowsiness. If these symptoms are ignored, muscular fatigue, muscle pains, gastric upset, oliguria, and hypotension may result. Finally, convulsions, coma, or a condition resembling "shock" may develop. The latter symptoms will never occur if the warning offered by earlier ones is not ignored.

With intensive or prolonged therapy, it is particularly important to guard against alkalosis (due to chloride depletion) and hypokalemia. In cardiac patients receiving digitalis, potassium depletion can be particularly hazardous. The sensitivity to digitalis is increased in the presence of depleted serum potassium, and heart block or other manifestations of digitalis intoxication may result. These conditions may result from excessive administration of ORETIC, and may be precipitated by dehydration (e.g., from vomiting) or severe salt restriction.

While therapy with ORETIC will often allow some relaxation of severe sodium restriction, it is also true that sodium restriction reduces the need for diuretic therapy. Thus, dosage of ORETIC and sodium intake must be considered together and mutually adjusted for maximum benefit.

The "low salt syndrome" has not been reported as occurring during ORETIC therapy. Yet the possibility should be kept in mind, especially if heavy dosage is employed together with severe sodium restriction in a very edematous patient. When frequent massive doses of ORETIC are employed, it is recommended that serum sodium levels should be followed by means of laboratory studies. If facilities are not available, the

patient should be allowed a moderate amount of sodium (one gram or more) in the daily diet. It is of interest that the administration of some salt in a patient in whom serum sodium levels are low, may actually help to initiate diuresis.

An occasional hypertensive patient who receives ORETIC may show some evidence of nitrogen retention. This can be expected to occur only in patients whose blood pressure is markedly reduced. It seems probable that the causative factor is the lowering of the blood pressure, which in turn produces reduced blood flow through impaired kidneys. Under these conditions, the kidneys are no longer able to eliminate the excess nitrogen, but are often able to do so if the reduced blood pressure is allowed to rise toward the previous levels.

In patients with cirrhosis and ascites, chlorothiazide has been observed to produce symptoms of impending hepatic coma (confusion, drowsiness and tremor).[6] In this study it was suggested that impending hepatic coma could be prevented by the simultaneous administration of broad-spectrum antibiotics. Similar effects could be anticipated following the administration of ORETIC to patients with impaired liver function. If laboratory tests reveal the presence of ammonia intoxication, it should be treated by the usual methods.

If the possibility of hepatic coma, hypokalemia and alkalosis are kept in mind, cautious administration of ORETIC may produce benefit in some patients with cirrhosis and ascites. However, in these cases, potassium chloride administration should be considered on a routine basis, and a careful watch must be kept on the patient's general condition and laboratory findings.

Specific side effects following the administration of ORETIC have been infrequent. They have included occasional reports of nausea, skin rash, anorexia, headache, restlessness, fatigue and constipation. Side effects of this type can often be overcome by lowering the dose or administering the drug following a meal.

ORETIC | CLINICAL STUDIES

Results following the administration of ORETIC have been uniformly favorable. Effectiveness and tolerance have been carefully assessed in patients with edema who had a variety of diagnoses including congestive heart failure, nephritis, nephrosis, diabetes, Raynaud's disease, premenstrual tension, glaucoma, obesity and hypertension of various types. Laboratory studies, in addition to clinical indications, have confirmed the safety of this type of therapy.

In general, side effects (even from large doses) have been few. Elimination of edema fluid has been prompt and usually complete. Control of hypertension has been facilitated, both in mild cases in which ORETIC has been effective when used alone, and in more severe cases when it has enhanced the action of other hypertensive agents. In some instances, the dosage of ganglionic blocking agents has been lowered by as much as 50 percent when their use has been combined with administration of ORETIC. Some patients refractory to mercurial diuretics and chlorothiazide have shown a good response after administration of ORETIC.

Laboratory studies have indicated that comparatively small doses of ORETIC have markedly increased the excretion of water sodium chloride. Excretion of potassium and bicarbonate has also been increased, but to a much lesser degree. In many cases potassium levels have remained relatively unaffected.

PUBLISHED REPORTS The clinical effectiveness of heterocyclic oral diuretics has been well documented.[7-11] These agents have properties similar to both carbonic anhydrase inhibitors and the mercurial diuretics.

Pitts and his associates[12] have pointed out that the molecule in this type of compound contains "a free sulfonamyl group, and consequently "it inhibits carbonic anhydrase *in vitro* and in large doses *in vivo*, alkalinizes the urine, and increases the urinary excretion of potassium. In addition it causes naturesis and chloruresis, actions similar to those of

mercurial diuretics." There is also evidence of an additive action when ORETIC is administered together with mercurial diuretics.

Herrmann[18] presented the results of a study with hydrochlorothiazide at the Texas Academy of Internal Medicine in December, 1958. He and his associates studied 21 patients suffering from edema. In 20 patients the cause was congestive heart failure; in 1 patient it was undetermined.

Detailed laboratory and clinical studies were carried out on all patients. The authors found hydrochlorothiazide "to be a clinically effective oral diuretic which is well tolerated."

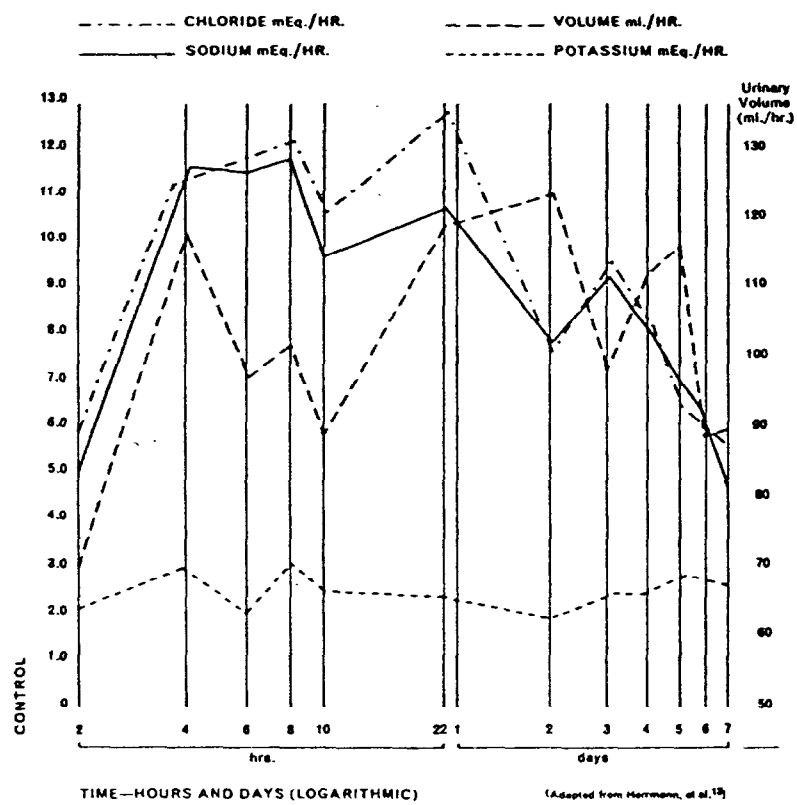
Other conclusions from this study were as follows:

- "The diuretic effect appears to be similar to that of the mercurials, in that urinary volume is augmented, with predominantly an excretion of sodium and chloride to about three times the control levels. Potassium excretion was increased slightly, to a maximum increase of 30 percent in these short-term studies."
- "The dosage necessary was one-fourth to one-eighth that of chlorothiazide, and so milligram for milligram (hydrochlorothiazide) is the most effective diuretic that we have used."
- "A single dose of 200 mg. produces a diuresis which begins about two hours after one ingestion, and is maintained for more than 24 hours. Effective diuresis can also be achieved by 50 mg. doses administered twice daily."
- "On the basis of a limited number of cases, the anti-hypertensive action of (hydrochlorothiazide) appears promising. However, the matter of nitrogen retention calls for care in long-term therapy in hypertensive patients, especially those with renal disease, just as is the case with chlorothiazide."

Average values for the excretion of urine and electrolytes following the administration of hydrochlorothiazide to 14 patients included in this study are shown in the accompanying graph.

OUTPUT OF URINARY VOLUME AND ELECTROLYTES

AVERAGE VALUES FROM 14 HOSPITALIZED PATIENTS RECEIVING HYDROCHLOROTHIAZIDE



UNPUBLISHED REPORTS A number of investigators have evaluated various aspects of therapy with ORETIC. In one study, patients under treatment with mercurials or chlorothiazide were transferred to hydrochlorothiazide in order to determine relative potency. The 50 patients selected were suffering from congestive heart failure and response was evaluated on the basis of serum potassium levels, weight and serial electrocardiograms. Eighty percent showed marked improvement with an average weight loss of 9 pounds on being transferred to therapy with hydrochlorothiazide. An equivalent dosage relationship appeared to be approximately 150 mg. of hydrochlorothiazide, as against 1000 mg. of chlorothiazide.

Another report was based on evaluation of 60 patients with edema from a variety of causes. Twenty-two patients suffering from obesity (under treatment with amphetamine and restricted diet) showed a very good weight loss when hydrochlorothiazide was used as a supplement in treatment. A number of patients suffering from premenstrual tension also responded well to this therapy. Side effects were mild and infrequent, and consisted only of nausea in a few cases.

Other reports have indicated a good clinical response in hypertensive patients with or without congestive failure. Significant reductions in blood pressure have occurred when ORETIC has been used alone. Reports have indicated a marked ability of ORETIC to potentiate the effect of other anti-hypertensive agents, such as rauwolfia derivatives, hydralazine, veratrum alkaloids and ganglionic blocking agents.

ORETIC | PHARMACOLOGY

TOXICITY Hydrochlorothiazide has a high therapeutic ratio (greater than 1:1000 in the dog and rat) and has a very low toxicity. In dogs, daily doses up to 60 mg./Kg. were well tolerated for periods up to four weeks.

The poor solubility of hydrochlorothiazide in water makes it difficult to determine a true LD_{50} by either the oral or intravenous routes. In

rats, a 10 percent solution in 80 percent N,N-dimethylacetamide was injected intravenously. The LD_{50} for this mixture was greater than 350 mg./Kg. but the specific effect of the hydrochlorothiazide could not be determined because of the toxicity of the N,N-dimethylacetamide. However, no symptoms developed which could be directly attributed to the hydrochlorothiazide *per se*.

The oral LD_{50} of hydrochlorothiazide in the rat was greater than 2.7 grams/Kg. The amount which could be administered was limited by the poor solubility of the drug in water and by the amount which could be ingested at one time.

Dogs have tolerated hydrochlorothiazide at a dosage of 100 mg./Kg. by the intravenous route (as a 10 percent in N,N-dimethylacetamide) and at a dosage of 1 gram/Kg. orally. The intravenous administration produced transient ataxia and vomiting. There were no toxic symptoms following the oral administration.

In all species of laboratory animals hydrochlorothiazide was well absorbed following oral administration. Diuretic activity started promptly, was maximal within approximately three hours, and persisted for four to six hours or longer.

Studies indicated that the drug was eliminated by the kidney although glomerular filtration rate and renal plasma flow were not significantly altered. In animals with normal blood pressure, there was no change, but in hypertensive animals some effect on blood pressure was noted. Chronic toxicity studies employing 750 mg./Kg./day in rats and 250 mg./Kg./day in dogs have been carried for many months without the development of toxic symptoms.

PHARMACOLOGIC EFFECTS Comparative experiments in dogs have indicated that hydrochlorothiazide possesses a longer duration of action than chlorothiazide. A similar relationship can be demonstrated in rats.

Hydrochlorothiazide appears to have no effect on carbohydrate metabolism, but does show an inhibitory effect on carbonic anhydrase at

relatively low concentrations.

In normal anesthetized and unanesthetized dogs, hydrochlorothiazide did not show any effect on blood pressure, heart rate, or pulse pressure. In the anesthetized dog, it did appear to potentiate the action of hydralazine in producing a reversal of the epinephrine effect.

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12. Pitts, R. F., et al., J. Pharmacol. and Exper. Therap., 123:89, June, 1958.
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The CHAIRMAN. Now, you have an exhibit B on Oretic. Would you want that in the record?

Mr. CAIN. It would be pertinent, Mr. Chairman, because it substantiates the statement regarding the ad that appeared, the eight-page ad.

The CHAIRMAN. That will be received in the record.

(The document referred to is as follows:)

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ETIC ACT

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Would you

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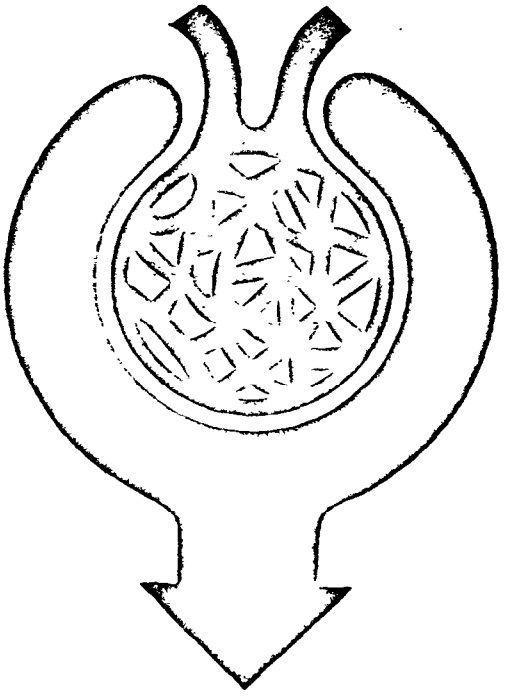
EXHIBIT B

PRESENTING A SPECIAL NEW-PRODUCT REFERENCE ON

ORETIC™
(HYDROCHLOROTHIAZIDE, ABBOTT)



YOUR MOST POTENT MEANS
WHEN THE END IS SALURESIS®

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ORETIC INTRODUCTION

Doctor: In simplest terms, prescribing new ORETIC is like packaging a low-salt regimen in a single tablet . . . because ORETIC steps up excretion of sodium and chloride, and thereby often cuts down the need for an extremely rigid low-sodium or salt-free diet.

It follows that the more potent the diuretic-antihypertensive, the greater the chances that sodium restrictions can be relaxed.

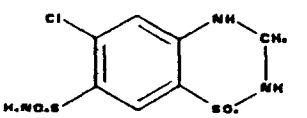
And new ORETIC is the most potent oral diuretic-antihypertensive yet discovered. It has a high therapeutic ratio, low toxicity. It works successfully with dosages only 1/10—1/12 those of chlorothiazide.

The following pages of product information . . . indications, dosage, precautions and clinical reports . . . are presented here to give you useful facts about the application of new ORETIC—not only to low-salt therapy but to all other conditions in which this potent drug could conceivably be your agent of choice.

ORETIC WHAT IS IT

ORETIC is the Abbott trademark for hydrochlorothiazide, a synthetic heterocyclic compound possessing diuretic properties. This agent enhances the excretion of sodium and chloride by a direct action on the renal tubules. It also inhibits the action of carbonic anhydrase. It is as effective as chlorothiazide, but at considerably reduced dosage—from 1/10—1/12 of the dose of the parent compound.

ORETIC is a white, crystalline solid, which is slightly soluble in cold water or alcohol, and more readily soluble in alkaline solutions. Chemically, it is 6-chloro-3,4-dihydro-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide, and has the following structural formula:



ORETIC INDICATIONS

There are two primary indications for the use of ORETIC . . . the elimination of excess fluid (edema from any cause) and the treatment of hypertension. ORETIC may be used alone in mild cases of hypertension or in combination with other antihypertensive agents such as Harmonyl®.

ORETIC EDEMA

RENAL EDEMA ORETIC is of value in the management of nephrotic edema caused by various forms of renal disease. *Its employment may reduce the necessity for very rigid sodium restriction usually required when ACTH or steroids are administered.* However, severe renal impairment may render kidneys unresponsive to any form of diuretic therapy. If response is not ob-

®Harmonyl—Deserpidine, Abbott

tained, and if clinical and laboratory studies indicate progressive renal failure, therapy with ORETIC should be discontinued.

CARDIAC EDEMA In congestive heart failure ORETIC produces a copious diuresis comparable to that produced by parenterally administered mercurials. The potency, long-term effectiveness and safety of ORETIC make it an agent of choice for maintenance therapy in cases of cardiac failure. Symptoms such as dyspnea, orthopnea and chronic cough may be dramatically improved. ORETIC *may reduce the necessity for salt restriction, and is thus particularly useful in patients who find it difficult to follow a salt-free diet.* If desired, ORETIC may be used together with mercurial diuretics, though this is seldom necessary. It should be remembered that successful employment of diuretic agents does not eliminate routine measures in the treatment of heart disease such as rest, digitalization and careful attention to the diet.

TOXEMIA OF PREGNANCY ORETIC is especially useful when salt and fluid retention present a problem. It should be used as an adjunct to the usual measures and, if necessary, may be combined with more potent antihypertensive drugs. The dosage of these is generally reduced when ORETIC is employed, and danger of toxic side effects is thereby minimized.

PREMENSTRUAL EDEMA, EDEMA IN PREGNANCY Small doses of ORETIC are often useful in overcoming the antidiuretic effect which may be seen, in some patients, in the above conditions.

STEROID EDEMA The administration of adrenal and pituitary hormones (ACTH, cortisone, hydrocortisone, etc.) may be accompanied by salt or water retention leading to clinical edema. ORETIC may be successfully employed for the treatment of these secondary effects and may eliminate the need for cessation of steroid therapy.

ORETIC HYPERTENSION

ORETIC is indicated in the management of many cases of hypertension. *In mild cases, it can be used alone and will often eliminate the necessity for a rigidly-controlled salt-free diet.* In more severe cases it may be employed in conjunction with any of the standard antihypertensive drugs, including Harmonyl® and other rauwolfia derivatives, hydralazine, veratrum alkaloids and ganglionic blocking agents. It may also be of value, and produce improved control of blood pressure, in patients who have received a surgical sympathectomy.

ORETIC DOSAGE AND ADMINISTRATION

The adult dosage of ORETIC is in the range of 25 to 200 mg. daily. Usually, 75 to 100 mg. will produce the desired effect.

This may be given as a single dose in the morning, or if desired (particularly with larger doses) the tablets may be administered two or three times each day. Laboratory and clinical evidence indicates that ORETIC is as effective as chlorothiazide, but that the equivalent dosage is only 1/10—1/12 of the amount required with the latter agent.

ORETIC CONTROL OF EDEMA

ORETIC will frequently eliminate the necessity for parenteral administration of mercurials *and will often permit a reduction in rigid sodium restriction.* It may be given alone, or it may be used in combination with other agents for effective elimination of retained fluid.

Dosage should be adjusted in accordance with the patient's response. At the start of treatment 50 to 100 mg. may be administered after breakfast. If necessary this dosage may be repeated later in the day, and be administered twice daily for several days until the patient approaches dry weight.

When control of edema has been established, it may be maintained by daily or intermittent therapy with small doses. In some patients a daily dose as low as 25 mg. may be effective. In others, as much as 150 mg. may be required.

When regular therapy is employed, it is important to keep a careful and constant watch on electrolyte balance. Particular care should be taken to guard against potassium depletion. Patients on regular maintenance therapy should be instructed to take about 8 ounces of tomato, orange or citrus fruit juice two to four times daily. If this is impossible, potassium chloride may be administered by mouth at a dosage of 1 gram two to four times daily.

In many patients intermittent therapy is all that is necessary to maintain control of edema.

Thus, administration of ORETIC may be reduced to every second day, or to three to four consecutive days in each week. The optimum dosage as well as the time interval between administrations can only be determined by an individual trial in each patient. Intermittent therapy is generally recommended (when adequate) since this will reduce the possibility of producing electrolyte imbalance.

It is important to realize that the elimination of edema fluid does not necessarily cure the underlying disease or condition which caused the fluid retention. Appropriate treatment for the underlying cause of the edema should not be neglected.

ORETIC MANAGEMENT OF HYPERTENSION

At the start of treatment it is best to administer ORETIC early in the day. For the first few days some diuretic action may be apparent, and it is more convenient for the patient if this occurs during the waking hours. When fluid balance has adjusted, the diuretic action is not usually noticeable. Therefore, at the start of treatment, it is recommended that the total daily dose should be given after breakfast. For maintenance therapy, the daily dose can be divided and given two or three times a day. Dosage must always be individualized, but the following suggestions should provide guidance in establishing optimum benefit.

ORETIC USED ALONE

In mild cases of hypertension a satisfactory response may be obtained without the use of other antihypertensive agents. For initiating therapy, the average daily dose in the adult is 75 mg. After a few days the dosage should be adjusted upwards or downwards according to the response.

In general the maintenance dosage should be the minimum which will produce the desired effect on blood pressure. A maximum dose for maintenance is generally considered to be about 150 mg. daily. This may be divided and administered as 50 mg. t.i.d.

If blood pressure does not respond to ORETIC alone, therapy may be continued while other agents are added to the regimen.

ORETIC WITH HARMONYL OR OTHER RAUWOLFIA DERIVATIVES

ORETIC may be administered to patients receiving rauwolfia alkaloids without an initial alteration in the dosage of these compounds. After a few weeks the dosage of both agents may be reduced slowly until the minimum amount necessary to produce the desired benefit is established.

Adjustments in dosage should not be made too quickly since the action of rauwolfia derivatives is prolonged. Thus, the effect of a reduction in dosage may not become apparent for some weeks.

If the desired benefit has not been obtained, Harmonyl may be added to the regimen of the patient receiving ORETIC alone. Therapy with Harmonyl may be started at a daily dosage of 0.25 to 0.5 mg. (one or two tablets). The dosage may be revised according to the individual response. The combination of ORETIC with Harmonyl will often prove effective in lowering the blood pressure in patients who do not respond satisfactorily to either agent used alone.

ORETIC WITH OTHER ANTIHYPERTENSIVE DRUGS

It must be remembered that regular administration of ORETIC tends to make the patient more sensitive to the action of other antihypertensive agents. Therefore, if drugs such as hydralazine or ganglionic blocking agents are employed, initial dosage of these agents should be relatively small (approximately one-half of the recommended dosage when these agents are used alone). A satisfactory maintenance dose of the two agents can be established only by individual trial. Generally, the maintenance dose of the additional agent will be less when it is employed with ORETIC than when given alone.

ORETIC SUPPLIED

ORETIC tablets come in 25-mg. (List No. 6978) and 50-mg (List No. 6985) strengths, each in bottles of 100 and 1000.

ORETIC PRECAUTIONS AND SIDE EFFECTS

Since ORETIC is the most potent oral diuretic-antihypertensive available, it is to be expected that small doses will markedly increase the excretion of fluid and electrolytes. Therefore dosage and frequency of administration must be carefully adjusted to fit each patient. All patients should be observed closely for early signs of fluid or electrolyte imbalance. Precautions against potassium depletion were noted in the *Indications* section.

Early indications of electrolyte imbalance may include symptoms such as thirst, dryness of mouth, lethargy, weakness and drowsiness. If these are ignored, muscular fatigue, muscle pains, gastric upset, oliguria and hypotension may result. Finally, convulsions, coma, or a condition resembling "shock" may develop. The latter symptoms will never occur if the warning offered by earlier ones is not ignored.

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While therapy with ORETIC *will often allow some relaxation of severe sodium restriction, it is also true that sodium restriction reduces the need for diuretic therapy. Thus dosage of* ORETIC *and sodium intake must be considered together and mutually adjusted for maximum benefit.*

The "low-salt syndrome" has not been reported as occurring during ORETIC therapy. Yet the possibility should be kept in mind, especially if heavy dosage is employed together with severe sodium restriction in a very edematous patient. When frequent massive doses of ORETIC are employed, it is recommended that serum sodium levels should be followed by means of laboratory studies. If facilities are not available, the patient should be allowed a moderate amount of sodium (one gram or more) in the daily diet. It is of interest that the administration of some salt in a patient in whom serum sodium levels are low, may actually help to initiate diuresis.

An occasional hypertensive patient who receives ORETIC may show some evidence of nitrogen retention. This can be expected to occur only in patients whose blood pressure is markedly reduced. It seems probable that the causative factor is the lowering of the blood pressure, which in turn produces reduced blood flow through impaired kidneys. Under these conditions the kidneys are no longer able to eliminate the excess nitrogen, but are often able to do so if the reduced blood pressure is allowed to rise toward the previous levels.

In patients with cirrhosis and ascites, chlorothiazide has been observed to produce symptoms of impending hepatic coma (confusion, drowsiness and tremor).[1] In this study it was suggested that impending hepatic coma could be prevented by the simultaneous administration of broad-spectrum antibiotics. Similar effects could be anticipated following the administration of ORETIC to patients with impaired liver function. If laboratory tests reveal the presence of ammonia intoxication, it should be treated by the usual methods.

If the possibility of hepatic coma, hypokalemia and alkalosis are kept in mind, cautious administration of ORETIC may benefit some patients with cirrhosis and ascites. But in these cases, potassium chloride administration should be routinely considered, and careful watch kept on the patient's general condition and laboratory findings.

Specific side effects following the administration of ORETIC have been infrequent. They have included occasional reports of nausea, skin rash, anorexia, headache, restlessness, fatigue and constipation. Side effects of this type can often be overcome by lowering the dose or administering the drug following a meal.

ORETIC CLINICAL STUDIES

Results following the administration of ORETIC have been highly favorable. Effectiveness and tolerance have been carefully assessed in patients with edema who had a variety of diagnoses including congestive heart failure, nephritis, nephrosis, diabetes, Raynaud's disease, premenstrual tension, glaucoma, obesity and hypertension of various types. Laboratory studies

as well as clinical indications have confirmed the relative safety of this type of therapy.

In general, side effects, even from large doses, have been few. Elimination of edema fluid has been prompt and usually complete. Control of hypertension has been facilitated both in mild cases in which ORETIC has been effective when used alone, and in more severe cases when it has enhanced the action of other hypertensive agents. In some instances the dosage of ganglionic blocking agents has been lowered by as much as 50 per cent when their use has been combined with administration of ORETIC. Some patients refractory to mercurial diuretics and chlorothiazide have shown a good response after administration of ORETIC.

Laboratory studies have indicated that comparatively small doses of ORETIC have markedly increased the excretion of water sodium chloride. Excretion of potassium and bicarbonate has also been increased, but to a much lesser degree. In many cases potassium levels have remained relatively unaffected.

The clinical effectiveness of the heterocyclic oral diuretics has been well documented.[2-4] These agents have properties similar to both carbonic anhydrase inhibitors and the mercurial diuretics.

Pitts and his associates[7] have pointed out that the molecule in this type of compound contains a free sulfonamyl group and consequently "it inhibits carbonic anhydrase *in vitro* and in large doses *in vivo*, alkalinizes the urine and increases the urinary excretion of potassium. In addition it causes naturesis and chloruresis, actions similar to those of mercurial diuretics." There is also evidence of an additive action when ORETIC is administered together with mercurial diuretics.

Hermann[8] presented the results of a study with hydrochlorothiazide at the Texas Academy of Internal Medicine in December, 1958. He and his associates studied 21 patients suffering from edema. In 20 patients the cause was congestive heart failure; in 1 patient it was undetermined.

Detailed laboratory and clinical studies were carried out on all patients. The authors found hydrochlorothiazide "to be a clinically effective oral diuretic which is well tolerated."

Other conclusions from this study were as follows:

"The diuretic effect appears to be similar to that of the mercurials, in that urinary volume is augmented, with predominantly an excretion of sodium and chloride to about three times the control levels. Potassium excretion was increased slightly, to a maximum increase of 30 per cent in these short-term studies."

"The dosage necessary was (considerably less than) that of chlorothiazide, and so milligram for milligram (hydrochlorothiazide) is the most (potent) diuretic that we have used."

"A single dose of 200 mg. produces a diuresis which begins about two hours after one ingestion, and is maintained for more than 24 hours. Effective diuresis can also be achieved by 50 mg. doses administered twice daily."

"On the basis of a limited number of cases the anti-hypertensive action of (hydrochlorothiazide) appears promising. However, the matter of nitrogen retention calls for care in long-term therapy in hypertensive patients, especially those with renal disease, just as is the case with chlorothiazide."

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The CHAIRMAN. It may be that the print referred to on the last page, we may have some difficulty in getting that in the record, I am not sure that we can, but we will see about it.

Mr. CAIN. If it is possible, for the purpose of completeness only, Mr. Chairman, it brings out the point of completeness of the information furnished to the physician which I think at least partly answers the question you raised earlier in the afternoon.

The CHAIRMAN. Yes, but I merely caution that I am not sure that this last page can be printed. I doubt it. Now you have exhibit C.

Mr. CAIN. We can supply an original of that, Mr. Chairman, which will be more clear.

The CHAIRMAN. We will receive it and if it can be included in the record we will try to do it, but otherwise you will understand why.

Mr. CAIN. Yes, sir.

(The document referred to is as follows:)

EXHIBIT C
(J.A.M.A., October 22, 1960)

OLD SALT

(or, How to chart a course to brighter diets in edema and hypertension)

Man, food and salt: a satisfying triumvirate. Yet the edema or heart patient may be denied this pleasant union every day. He eats, but without the bright touch salt brings. *Small loss? Certainly.* Still, small losses often loom large in the patient's mind. A good diuretic like Oretic can help out here. *Oretic will successfully treat edema, and work well in mild to moderate hypertension.* It produces a generous elimination of water and sodium. And this latter saluretic effect often opens the door *to a more liberal low-sodium regime. Not every time, naturally. Each patient—each diet—* is different. But an adjusted diet should be possible often enough to make the plan worth considering. *Consider what it will mean to the patient to have the real pleasure of some real salt back on the table.* You'll know how much it means, when he thanks you.

ORETIC (Hydrochlorothiazide, Abbott) a potent means when the end is saluresis. Tablets, 25- and 50-mg.

The CHAIRMAN. And then exhibit D, that may be all right for some people. I am not sure that the Congress will get much benefit out of that.

Mr. CAIN. No, sir, but it shows the completeness, Mr. Chairman. That is the point we are trying to bring out.

The CHAIRMAN. Let it be received, exhibit D. I think we will have a little difficulty in reading a few pages in this, but it does refer to a good many articles that may be of interest.

Mr. CAIN. Thank you, sir.

(The document referred to is as follows:)

EXHIBIT D (Part I)

HYDROCHLOROTHIAZIDE: DOMESTIC CLINICAL REFERENCES
Jan. 1957 - Sept. 1960

Am. Med. A., Council on Drugs
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Barrett, W.E., et al.
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Chlorothiazide and hydrochlorothiazide; a comparative study of their hypotensive, saluretic and hyperuricemic action. Ann. Int. Med. 53:342-58, Aug. 1960.

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Etiology and therapy of essential hypertension. A review. J. South Carolina M.A. 56:171-5, May 1960. (A comprehensive therapeutic regimen includes hydrochlorothiazide and Rauwolfia therapy.)

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Newer approaches to antihypertensive therapy. J.A.M.A. 172:1041-4, Mar. 5, 1960. (Discusses specifically those newer compounds which (1) affect

catecholamine release, (2) alter fluid and electrolyte balance, and (3) interfere with enzymatic activity.)

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Treatment of severe hypertension. J. Iowa M. Soc. 50:485-91, Aug. 1960. (Drug therapy includes: Rauwolfia compounds, hydralazine, thiazide derivatives and ganglion-blocking agents.)

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Effect of hydrochlorothiazide (Esidrex) on intraocular pressure in man. Am. J. Ophth. 49:1321-4, June 1960. (Oral administration of hydrochlorothiazide in single doses of 50 to 150 mg. produced a slight decrease in intraocular pressure in nonglaucomatous and glaucomatous eyes of humans. Its use primarily for the control of glaucoma is not recommended.)

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The ideal diuretic. Current Therap. Res. 2:30-1, Jan. 1960. (An editorial) (Comparative potency of hydrochlorothiazide and chlorothiazide.)

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Evaluation of 3-benzylthiomethyl chlorothiazide, a new oral diuretic. Clin. Pharmacol. & Therap. 1:175-9, Mar.-Apr. 1960. (A clinical evaluation is presented of the relative diuretic effectiveness of benzylthiomethyl chlorothiazide and hydrochlorothiazide in 17 edematous patients. Comparing single

100 mg. doses of each drug, benzylthiomethyl chlorothiazide is about 85 per cent as effective as hydrochlorothiazide.)

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The choice of a diuretic with special reference to hydrochlorothiazide. J. M. A. Georgia 48:389-93, Aug. 1959.

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Hydrochlorothiazide and syrosingopine in the control of hypertension. J. Am. Geriatrics Soc. 8:803-5, Aug. 1960.

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LIBRARY ABBOTT LABORATORIES. NORTH CHICAGO. ILLINOIS
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SCOPE OF SEARCH

Source	Time	Subjects
CIML	July 1958 - Dec. 1959	Congestive heart failure Edema Heart diseases Hypertension Hypertension, postural Chlorothiazide Chlorothiazide, Clinical (and Hydrochlorothiazide)
Library Bib. file Abbott Abstracts-IBM search	1957 - Dec. 1958	

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SQ & JDK/mn

The CHAIRMAN. And then the memorandum attached which has already been received for the record.

I made a notation on page 12 of your statement with reference to additional safeguards, and the suggestion that this particular statement be included in the advertisement. Do you think that would do any good at all?

Mr. CAIN. Well, I think, Mr. Chairman, that there is a feeling on the part of some people that perhaps some such reference might be included. I think personally that if you take in toto all of the available sources of information that are available to the physician, and keep in mind always that the physician does not prescribe drugs for use of his patients until he has made himself familiar with the drug, its background and all about it, then I think this is superfluous.

The CHAIRMAN. You say before prescribing. I assume that means by the doctor, doesn't it?

Mr. CAIN. Yes, sir.

The CHAIRMAN. It seems to me that the medical profession might take that as sort of an insult.

Mr. CAIN. We think that the medical profession could well take it as an insult, Mr. Chairman.

The CHAIRMAN. In other words, you are deliberately trying to insult them?

Mr. CAIN. Perhaps we are bowing to a little pressure from other sources.

The CHAIRMAN. Mr. Schenck, any questions?

Mr. SCHENCK. Thank you, Mr. Chairman. I am very much interested in Mr. Cain's statement. Now on page 5 I was wondering if this was an error. In the last paragraph in line 4 you say: "Furthermore, the FDA regulations do not require full disclosure in the package insert." Is this a correct statement?

Mr. CAIN. In certain instances, yes, sir.

Mr. SCHENCK. I thought FDA did require full disclosure in the package inserts.

Mr. CAIN. Well, if you go on, Mr. Congressman, it says "when drug directions, hazards, and warning uses are commonly known to licensed medical practitioners."

In other words if you take a well, old established drug, there are certain exceptions as I recall now that do not require these regulations. In other words, he knows so much about it that there is little if anything that can be added.

Mr. SCHENCK. That is quite all right. I wondered if it was an error in your statement.

Mr. CAIN. No, sir. I am glad you brought it up but it is accurate.

Mr. SCHENCK. Now, Mr. Cain, there seems to be a growing tendency by certain pharmacists to advertise prescription drugs in the local press of the community. These drugs can be purchased only through a prescription of the physician and not in the quantities advertised in the local advertisements, which I have in a number of cities. Do you care to make any statement on that?

Mr. CAIN. The only comment I can make on that is that I am accurate in this, that some outlets will advertise in local media: "Bring your prescriptions here." The purport of the advertisement: "We will fill them more cheaply than normally would be available to you from your normal source."

That, I suppose, is a form of competition at that level that exists, and I presume that that would be the choice of the individual proprietor or owner of that particular outlet. I don't think that that necessarily means that there is anything wrong with it, nor that there perhaps would be inferior drug supplies.

But maybe that particular man's overhead is lower; I don't know. That form of competition does exist and that is about the only comment I can make on it.

Mr. SCHENCK. I am thinking of such a drug as amphetamines here which you mentioned in your statement.

Mr. CAIN. Yes.

Mr. SCHENCK. Now that is a drug which I understand can be purchased only as a result of a physician's prescription.

Mr. CAIN. Yes, sir.

Mr. SCHENCK. Yet if a local store advertises that at so much per hundred, perhaps the physician limits it to 25, I just wondered if the pharmaceutical society has a position on that.

Mr. CAIN. The patient would still have to present the written prescription of his physician to be filled by this type of an outlet that you are talking about.

Mr. SCHENCK. Yes.

Mr. CAIN. If the prescription read "for only 25," that would be all that that prescription could authorize. He could not obtain a bottle of 100 legally.

Mr. SCHENCK. I knew that of course, but I was wondering what would be the advantage in advertising such prescription drugs on this basis.

Mr. CAIN. Cutrate drugs. I mean they advertise that in the papers on Sunday morning.

The CHAIRMAN. Mr. Dingell.

Mr. DINGELL. Thank you, Mr. Chairman.

Mr. Cain, I would like to welcome you before the committee. You are well vouched for by my good friend Mr. Harrold B. Jones, who speaks very highly of you.

Mr. CAIN. Thank you, Mr. Dingell.

Mr. DINGELL. I hope you won't think it is unkind of me if I ask you a few questions, since you made a few comments on portions of this bill of which I happen to be the principal sponsor. I notice that you have inserted into medical periodicals the number of ads which you submitted to this committee, the first of which is a full page in one on "fast acting Nembutal."

Mr. CAIN. Yes, sir.

Mr. DINGELL. Now in this ad you take up a full page. It comes from the "Current Medical Digest and Annals of Surgery," February 1961. You also list some others in approximately an 8 by 10 or 8 by 12 size page, and on this appears these words "fast-acting Nembutal (Pentobarbital, Abbott), Nembutal rapidly produces cerebral depression of any desired degree, depending upon the dose." And then way down the bottom in small letters appear the numbers "102194."

Now, you used a whole page to tell the reader just those things. Why couldn't you put on there contraindications and side effects too without any undue hardship on Abbott, which is a very fine corporation.

Mr. CAIN. I think that we go back, Mr. Dingell, to the principle that this is simply and only intended to be reminder advertising.

Mr. DINGELL. I see. Now in another one you put down here in a full page in Resident Physician, Medical Economics, and New Physician, you put a two-page ad and on one side of the page the only thing you show is you are talking about Compocilin V-K (Potassium Penicillin V) Granules for Oral Solution. This is one one side. On the other side you have a picture of a box of cherries, a spoon and these words "Now in a pleasing cherry oral solution, the high blood levels of Potassium Penicillin V."

Now why couldn't you on that page put down the side effects and contraindications?

Mr. CAIN. Because we chose again to use this medium as reminder advertising. We keep getting back to that point.

Mr. DINGELL. Another one here, a two-page ad, on one side you talk about Oreticyl. One one side you have Oreticyl——

Mr. CAIN. Yes, sir.

Mr. DINGELL. "Just one prescription for new Oreticyl," and you have a picture of a man unloading a truck that takes up three-quarters of the page.

Now, certainly, it would not be any hardship for you to apprise the physician who is going to look at this of the side effects on this, especially since in the one on Oreticyl you came out and you said:

> This is because * * * it lowers blood pressure without producing excess side effects.

Then you say:

> When Harmonyl, Abbott's unique rawolfia alkaloid is combined with the potent diuretic antihypertensive Oretic, the result is convenient, efficient, one-tablet treatment especially suited to hypertensives who must remain alert and active during the day.

Then you go on and you say that it "produces elimination of water and sodium," so that in many cases it is helpful to low salt diets, and you go on.

Now, I do not want to burden you unduly with this piece of legislation, but it does seem to me that when you put out an ad this big with this little copy in it and you tell the good things about it, it seems like maybe in the interests of protecting the doctor and making life just a little easier for him you might give him a little bit of information as to the contraindications and side effects.

Mr. CAIN. Mr. Dingell, as I say and have said and will continue to say, we are merely using this form of medium as a form of reminder advertising to the doctor.

Now, he has full, complete data on this drug in various other mediums, example of which you have before you, plus medical journals, plus medical meetings, plus scientific exhibits.

He is well informed. He does not prescribe on the basis of reminder advertising.

Mr. DINGELL. If he reads all that you tell us about, when does he see his patients? That is the question. He is a busy man, you will concede?

Mr. CAIN. Of course, he is a busy man. He is also a learned and talented man, who is well educated and well grounded in his profession.

Mr. DINGELL. I recognize that, but the fact of the matter is it would not be an undue burden on him to have a quick rundown of the contraindications and side effects put into these remainder advertisements.

Mr. CAIN. Mr. Dingell, that is a point of view.

Mr. DINGELL. I see. Now, I note here that a substance by the name of Norlutin was advertised for 3 months in a Journal of the American Medical Association, 3 months after it was found that it had caused difficulties to children born of mothers who used it.

Mr. CAIN. We are getting into a medical area with which I am not competent to comment on. That is a drug of another house.

Mr. DINGELL. I know that, I am aware of that, and that is one of the reasons why I chose it rather than some of the others, because I did not want anything to reflect on anyone who was testifying here today.

Mr. CAIN. Well, I am not competent to judge on the merits of the drug or its use.

Mr. DINGELL. Here we have a situation where 3 months after this situation is found, the same advertisement continues, directed to the medical profession, without mention of this particular effect.

Now, do you not think that calls for some corrective action or for some redress or perhaps some reappraisal of the comments you have made to the committee today?

Mr. CAIN. Not in the slightest, because I am not familiar with the history of this, and I have to take your word for it.

Mr. DINGELL. Well, the interesting thing is this is in testimony on the hearings of another committee.

Now, let us go a little bit further, if we may, here. Are you familiar with the practice of using detail men in the industry?

Mr. CAIN. Am I?

Mr. DINGELL. Yes.

Mr. CAIN. I certainly am.

Mr. DINGELL. Do you know how many detail men there are?

Mr. CAIN. I do not know in total, but I think somewhere in the neighborhood, I would guess—I think this came out in earlier testimony—somewhere in the neighborhood of 15,000.

Mr. DINGELL. I have seen that figure used rather widely, and there are approximately 150,000 practicing physicians in the country; am I correct?

Mr. CAIN. I think closer to 160,000.

Mr. DINGELL. This is roughly a ratio of 1 detail man for every 10 physicians; am I correct?

Mr. CAIN. Yes.

Mr. DINGELL. Now, what controls does the industry impose on the detail men and what do you do with regard to representations that are made by them orally to physicians?

Mr. CAIN. I can only cite, Mr. Dingell, the experience in our own company.

I have forgotten who it was on the committee that asked the question earlier.

I think it was Mr. Schenck who asked about the quality of the detail men.

We try to obtain men with backgrounds in pharmacy or premedicine or chemistry. Those men, before they are ever put into the field, are brought into the home office and given a period of intensive train-

ing by our medical staff, by our research people, by our pharmacologists, on the different drugs that they will be detailing. They are then sent out under supervision of trained supervisors in the field. They receive weekly bulletins on information of a scientific nature on drugs, new developments, literature, so forth and so on. They are held strictly accountable for what they represent regarding our products, as well as competing products, and, quite obviously, based on your experience as well as mine, you quickly learn the people you can depend upon for accurate and thorough and reliable information.

Mr. DINGELL. Now, let me ask you this question——

Mr. CAIN. Pardon me, may I finish?

Mr. DINGELL. Certainly.

Mr. CAIN. They are also brought back for a period of periodic review, training, and instruction at frequent intervals of not less than every 2 years, and we have sales meetings at least once a year, mostly devoted to reinstructing these men as to what is happening, and they are brought up to date as to recent developments in medicine.

Mr. DINGELL. Now, in the field of securities, the sale of securities, I am sure you know that we license security dealers, and I am sure you are familiar with the fact that the Securities and Exchange Commission very closely supervises security salesmen?

Mr. CAIN. I understand that, but I am not familiar with it.

Mr. DINGELL. But there is no one other than the company which employs these men who supervised their qualifications, for example, whether they are registered pharmacists?

Mr. CAIN. We select the best men we can get and train them accordingly. It is our responsibility.

Mr. DINGELL. I am aware that your company does, but I am sure you are also aware that there are other companies that are not so ideally situated insofar as having means to secure competent people or some perhaps might not even have the inclination to secure——

Mr. CAIN. Mr. Dingell, I cannot sit and pass judgment on that statement.

Mr. DINGELL. I make the statement, but the simple fact of the matter is when a man wants to buy $100 worth of stock, he has to get it from a licensed broker-dealer, and if he wants to buy a $2 prescription, it may have come through a detail man who has no licensing supervision over him whatsoever; am I correct?

Mr. CAIN. The drug comes through the route, Mr. Dingell, of the pharmacist on prescription of the doctor, not through the detail men.

Mr. DINGELL. But what I am trying to find out is what scrutiny is given to what the detail man says when he visits the doctor behind closed doors?

Mr. CAIN. I have already told you that.

Mr. DINGELL. What supervision do we have over the claims that he might make on behalf of the drug?

Mr. CAIN. I have already answered that question, Mr. Dingell.

Mr. DINGELL. The best efforts that your company can make, I am sure, and I am sure that most other companies try to do the same thing, but what happens if he makes exaggerated claims and is not caught, or what happens if you receive no complaint on a matter of this sort, or what happens if, through some fluke, he gets in without proper supervision?

The problem is very real, is it not?

Mr. CAIN. Mr. Dingell, the doctor is an informed, intelligent, learned, practicing physician.

Now, if the man makes one mistake, the doctor is the first one that is not going to let him back in.

Incidentally, your problems in the security field are such that lately I notice in the paper we had a loss of $280,000 worth of securities.

Mr. DINGELL. Now, the other question I wanted to ask was:

Do you know what is spent on drug advertising in this country in total?

Mr. CAIN. Mr. Dingell, very fortunately, I was in the room this morning when you asked the question about Mr. Beesley's company.

Unfortunately, Mr. Beesley did not have the answer for his company, but I took the trouble to have one of our men who is down here with me to call North Chicago, and, for your information and only because I am here as a witness before the committee would I divulge this rather, what we would call, trade secret.

Last year our budget——

Mr. DINGELL. I did not ask for your company particularly, but I wanted the industry generally.

Mr. CAIN. I am glad to tell you. I do not have the industry information generally.

Last year our budget for journal advertising was $2,275,000, and, to complete that statement, our research expenditure was close to $11 million.

Mr. DINGELL. I am delighted to hear that.

Mr. CAIN. Thank you.

Mr. DINGELL. The reason is that the Senate Antitrust Committee came up with a figure that 24 cents on the sale's dollar was spent on advertising by the drug industry and 6.3 cents of the budget was spent for research.

Mr. CAIN. Mr. Dingell, there were some statements made in the statistical testimony of the Senate committee that I cannot quite agree with.

Mr. DINGELL. I am happy to hear that you set the record straight on your excellent company.

I appreciate your kindness in being before the committee today.

By the way, I noticed that when my bill, to which you referred in your testimony, was before this committee previously, that neither you nor any member of the Pharmaceutical Manufacturers Association appeared in opposition or submitted any testimony in opposition.

Mr. CAIN. We filed a letter, Mr. Dingell.

Mr. DINGELL. Oh, you filed a letter?

Mr. CAIN. Yes, sir.

Mr. DINGELL. But did not appear in opposition to the bill?

Mr. CUTLER. We filed the letter of Dr. Klumpp that is attached to Mr. Cain's statement.

Mr. DINGELL. I see.

I have a copy of the transcript, and it does not indicate that you were in opposition.

Mr. CUTLER. It would not show up in the transcript, sir, but it was filed on September 21, and I believe it will appear in your record when it is printed.

Mr. DINGELL. Thank you very much.

The CHAIRMAN. That presents another problem. You say it is not in the record of hearings of 1961?

Mr. CUTLER. I believe all that Congressman Dingell has is the typewritten transcript. We filed the letter on September 21.

The CHAIRMAN. Mr. Clerk, were those hearings printed?

Mr. WILLIAMSON. No, sir.

Mr. DINGELL. I believe the hearings were not concluded, Mr. Chairman.

I asked the same question.

The CHAIRMAN. If the letter referred to has not been included and it is not printed in this record, it should be printed in this record.

Mr. CUTLER. It would be most convenient to have it printed in this record, Mr. Chairman, because it relates so closely to this issue.

The CHAIRMAN. The two exhibits referred to a while ago that would become a part of this record by reference to those hearings will be included in this record.

I thought they were printed.

I did not see any need to print them twice.

If they have not been printed in the other record, let them be included in this one.

(The documents referred to are as follows:)

STATEMENT OF THEODORE G. KLUMPP, PRESIDENT OF WINTHROP LABORATORIES, ON BEHALF OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION ON H.R. 6471

My name is Theodore G. Klumpp. I am president of Winthrop Laboratories and a member of the board of directors of the Pharmaceutical Manufacturers Association. I was graduated from the medical school of Harvard University in 1928 and practiced at various hospitals in Boston, Cleveland, and New Haven, where I was on the faculty of the Yale University Medical School. In 1938 I became Chief of the Drug Division of the Food and Drug Administration and served in this capacity until 1941. I was vice president of the United States Pharmacopeia from 1950 to 1960 and was reelected to a second term running from 1960 to 1970. I also served as Chairman of the Medical Service Task Force of the Hoover Commission and am presently a member of the Medical Advisory Committee of the Department of Health, Education, and Welfare's Office of Vocational Rehabilitation. In addition, I was Chairman of the Office of Defense Mobilization's Task Force on Employment of the Handicapped.

The Pharmaceutical Manufacturers Association is a nonprofit membership association. Its membership includes approximately 140 companies engaged in the manufacture of ethical pharmaceutical and prescription drug products. These companies account for more than 95 percent of the Nation's total production of such items. No one company accounts for more than 10 percent of the total national output. My own company, Winthrop Laboratories, a division of Sterling Drug Inc., accounts for less than 3 percent of the total national output.

As we stated in our letter to this committee dated August 4, the Pharmaceutical Manufacturers Association supports the objective of full disclosure to physicians. On May 24, 1958, the association adopted a statement of principles of ethical drug promotion, by which our members pledged themselves to a policy of full disclosure to the medical profession with respect to our products. This statement of principles formalized as an industry policy what had long been the practice of the reputable manufacturers. We believe very strongly in this policy because we realize that a physician needs this information in order to fulfill his professional obligation properly when prescribing our products. We endeavor to disseminate this information through all appropriate channels. A copy of these principles is attached to my statement today.

The purpose of H.R. 6471 is to promote such disclosure. This purpose is entirely consistent with the established policy of the Pharmaceutical Manufacturers Association. Although we believe that the bill in its present form is extreme

and would be unworkable, we also feel that with certain modifications H.R. 6471 can be made to achieve its intended purpose.

Section 15 of the Federal Trade Commission Act now provides that if an advertisement of a drug to the medical profession sets forth the formula of the drug quantitatively it shall not violate the act unless the advertisement contains a false representation of a material fact. This section expressly provides that "labeling" of a drug is not advertising and, therefore, not subject to the jurisdiction of the Federal Trade Commission. These provisions of section 15 spring from congressional recognition that physicians constitute a special audience because they are all highly trained professional people. Moreover, these provisions reflect congressional awareness and appreciation of the unique role that the Food and Drug Administration plays for physicians by seeing that all relevant information concerning drug products is readily available to physicians in drug labeling. Thus, Congress, on the one hand, has charged the Federal Trade Commission because of its knowledge and expertise in advertising to see that advertisements to the medical profession contain no false statements. On the other hand, Congress has charged the Food and Drug Administration because of its knowledge and expertise in drugs to see, through the labeling of these products, that the medical profession is promptly, fully, and properly informed concerning them. This clear and express dichotomy of jurisdiction and function between the Federal Trade Commission (advertising) and the Food and Drug Administration (labeling) is based upon the realization of the precise role and purpose of the respective Federal agencies and reflects an abiding congressional wisdom.

H.R. 6471 would delete the foregoing provision of section 15 of the Federal Trade Commission Act dealing with advertisements of drugs that are disseminated only to the medical profession. It would also require that all advertisements of prescription drugs would be "misleading in a material respect" and, therefore, subject to suit by the Federal Trade Commission if they did not list the side effects and contraindications of the drug. In addition, H.R. 6471 directs the Commission to prescribe "such rules and regulations as may be necessary" to administer these provisions. Even though the side effects and contraindications of drugs are and have traditionally been reported in drug labeling in the amount of detail and often in the precise language required by the Food and Drug Administration, H.R. 6471 would make each advertisement of a prescription drug cover these same subjects in such detail and in such language as the Federal Trade Commission may deem necessary.

It is plain that H.R. 6471 seeks to make a radical change in congressional policy and this committee will, of course, give it the serious consideration that such a proposed change warrants. From the preceding analysis of the existing law and the provisions and effect of H.R. 6471 it would seem that the proponents of H.R. 6471 feel either that (a) the congressional recognition of the medical profession as constituting a special audience insofar as drug advertising is concerned is no longer warranted or (b) physicians are prescribing prescription drugs merely on the basis of advertisements about them and without consulting either their professional experience or available literature. We believe that neither of these assumptions is in fact valid.

No one needs to describe at length the very high and ever increasing standards of education and training that prevail in our medical schools and among our medical licensing boards and commissions. Likewise, the ever increasing and ever successful efforts of the Food and Drug Administration as well as nongovernmental groups such as the American Medical Association and the United States Pharmacopoeia to achieve full, prompt, and uniform disclosure, and dissemination to physicians, of all relevant information concerning drugs, their activities and effects certainly does not need to be described in detail to this committee. In addition, we note that, concerning physician's prescribing practices, the American Medical Association—the Nation's largest and leading association of physicians—has objected to this committee concerning H.R. 6471 that the physicians of America deem the allegation or implication that they are prescribing drugs without having sufficient information about them to be completely without foundation.

We shall now consider the particular provisions of H.R. 6471. After serious and full consideration of these provisions we feel that as presently written they fail to recognize the function of medical advertising and do not give sufficient weight and consideration to the other ways in which a physician gets his information about prescription drugs.

In various stages of my own career I have been a physician reading medical journal advertising and other information about drugs; I have been in charge of the Food and Drug Administration's Drug Division regulating what pharmaceutical companies must say and must not say to the physician in labeling their products; and I have been an officer of one of the companies being regulated. I hope that with this experience and with my experience as an officer of the United States Pharmacopoeia I can give you a balanced view of the problem of journal advertising and the effects that H.R. 6471 would have on this advertising and on the established lines of communication between manufacturer and physician.

The most important point is that medical journal advertising is only one of the physician's many sources of information about drugs. He is trained as a medical student and as an interne in the properties and utility of all the principal drugs then existing. In active practice, physicians supplement this training by regular reading of the medical journals, which publish disinterested evaluations of the newest drugs, written by toxicologists, clinical investigators, and others who write according to rigid standards of accuracy and objectivity.

In addition, the physician receives a wide range of information directly and indirectly from the pharmaceutical companies. With respect to new drugs these companies give physicians a full statement in brochure form of all available information concerning the product in question. Before releasing this brochure the company must submit it to the Food and Drug Administration. The final version reflects the views and modifications of the Food and Drug Administration and is disseminated as specified by the agency. In effect, this brochure is an approved documentary report of all aspects of the drug including indications, dosages, methods of use, clinical and other experience, side effects and contraindications. The size and content of these brochures will vary with each product. These brochures, of course, must be kept up to date. The procedure concerning the content and dissemination of revisions is precisely the same as the procedure outlined above for the initial brochure.

It is pertinent here to mention the recently announced plan of the American Medical Association and the United States Pharmacopoeia to put these brochures in uniform style, size, and format and to distribute them through their own facilities to physicians and pharmacists. This will go even further to assure that the physician has before him a handy and usable form all the information about side effects, contraindications and other matters that the Food and Drug Administration deems to be desirable.

This plan should be in effect next year and will undoubtedly increase the already great impact and authority of these brochures in the minds of physicians. In addition to brochures the companies send the physicians letters, samples and other detailed information concerning their products. They also have so-called detail men make professional visits in which they can answer the doctor's questions face to face, and provide him with any additional information he may desire.

The great majority of pharmaceutical companies are extremely careful in the information they transmit to doctors. They know that their most priceless asset is the confidence of the doctors in their integrity, a confidence built up by years of professional experience with the company's products and with the accuracy, objectivity and completeness of the information the companies supply to him. As a doctor and as a former Government official, I can affirm that the standard of integrity of the pharmaceutical companies matches the high standard of the medical profession and of the Government service.

Thus, entirely apart from what the physician reads in a medical journal advertisement, he has at his command from the manufacturer a vast quantity of detailed information about each drug whether it be a new drug or an old drug. In judging the accuracy and completeness of this information he may rely not only on the knowledge of the integrity of the particular manufacturer, but also on the close control exercised by the Food and Drug Administration.

I have brought with me these posters on which we have mounted all the information Winthrop Laboratories has furnished to doctors about two of its principal drugs, Hypaque, and Levophed. (At this point appropriate comments will be made describing each piece of material, including references to side effects, dosage, contraindications, etc.) [1] As can be seen from this exhibit it is virtually impossible, even if it were desirable, to include in an advertisement all

[1] When the witness appears before the committee he will introduce certain exhibits and describe them to the committee

the information concerning the indications, actions, warnings, side effects, contraindications, etc. Thus, any suggestion or implication in the advertisement to the effect that it does tell the whole story would in most cases be misleading to the detriment of the physician and his patient. A substantial portion of drugs cannot be properly and safely administered without accurate knowledge on the part of the physician of extensive directions for use, contraindications and possible untoward effects. Full information concerning these points can be presented not infrequently only in several pages of written matter. Who is to judge what excepted portion of this information is enough to satisfy the varying needs of practicing physicians? For one patient of a physician, one direction or warning may be vital, for another, some other portion of the whole story may be critically important. Anything less than the whole story may only succeed in conferring a false sense of security and because of this a simple reminder advertisement may be transformed into something that can be misleading. I need not remind this committee that a little knowledge is a dangerous thing and that anything less than the whole truth may do more harm than good. Yet, in its day-to-day practical applications, H.R. 6471 would require that "the partial story" be presented as if it were, in fact, "the whole story." Moreover, these requirements of H.R. 6471 would tend to undermine the traditional and highly effective means of communicating such information to physicians thereby impeding the current and planned efforts of the Food and Drug Administration and others to make the traditional system even more effective and reliable.

With this background, I hope the members of the committee will be able to appreciate the role of medical journal advertising in its proper relationship to the other information which the physician receives from the manufacturer and other sources. The medical journal advertisement is primarily intended as a reminder. It calls the physician's attention to a drug about which he already possesses detailed written information. As the American Medical Association has pointed out in its letter concerning H.R. 6471, no physician does or should prescribe a drug solely on the basis of what he reads in a medical journal advertisement. By the same token, no physician relies on a medical journal advertisement to include all the pertinent information about a drug that he requires in order to prescribe it. Thus such advertisements cannot and should not be judged by the standards of an SEC prospectus, as if it were the only or even the principal source of the doctor's information about a drug. Those who urge that medical advertisements should be judged by the standards of an SEC prospectus are impliedly attacking the physicians' professional reliability and integrity.

Once the proper role of medical journal advertising is understood, it becomes readily apparent that there are important practical limitations upon what the pharmaceutical manufacturer should be required to include in the advertisement:

(*a*) First and foremost, the advertisement obviously cannot include all the pertinent information about a drug that is relevant to a doctor's decision on whether to prescribe it. A medical journal advertisement is usually a half page or a full page in size. Smaller companies may only be able to afford a quarter page or less. From the poster I have shown you it is obvious that all of the pertinent information which the company supplies to the physician—and which the Food and Drug Administration properly requires him to supply—cannot possibly be printed on a quarter page, a half page or a full page, except in type so small that it cannot or will not be read. The problem is very much like trying to print the Declaration of Independence on the head of a pin.

(*b*) Apart from the physical limitations on the amount of information that can be squeezed into a medical journal advertisement, there is the problem of readability. There is no law requiring pharmaceutical companies to buy advertisements in medical journals. They are bought only because they perform a commercial function—the function of calling attention to a drug about which the doctor has already been informed through other means of communication. They will perform this function only if they attract the doctor's eye and if the copy can be readily perused. If the copy is too long, he will not read it any more than you or I would read the details of an insurance policy or of an SEC prospectus if they were crammed into an advertisement. The advertiser soon learns whether or not his advertisements are read. When they are not, he discontinues such advertising. Like most practicing physicians, I have a limited amount of time for medical reading. The general custom is to glance through the advertisements and devote most of the available reading time to the scientific articles. If the advertisements are clogged with detailed reading matter, like my colleagues, I won't bother to read them at all.

(c) In this connection, it should be noted that pharmaceutical advertising is the principal source of income of the medical journals. The scientific articles appearing in these jounrals are one of the most important sources of current education for the medical specialist and general practitioner. In my opinion, the proposed requirements placed on medical journal advertising will serve to destroy the commercial function of such advertising. This means inevitably that many of the medical journals will be forced out of business. If this happens, a valuable source of medical knowledge would be lost to the profession. As an example, I have attached a copy of an article in the New York Times of August 18, 1961, announcing the demise of Medical News, a weekly newspaper of the medical profession, because of advertising cutbacks by manufacturers.

In addition, a decrease in the number of medical journals without question will result in a serious delay in bringing important scientific communications to the attention of the medical profession. A personal experience may be cited to illustrate the point. In 1927 when the number of medical journals were fewer, I reported the discovery of the successful treatment of sprue, a fatal disease. Because of the backlog of papers awaiting publication, it took 9 months for the article to appear in print. No one can say for certain but it is likely that some patients with sprue died because of this delay. If the number of journals is seriously reduced, it can also be forecast that many scientific communications will never be printed because the existing journals will be forced to reject scientific papers to hold their own pages to manageable proportions. Thus, medical journal advertising serves a valuable function in bringing scientific reports promptly to the attention of physicians. Your committee will want carefully to weigh these serious adverse effects on medical communication which passage of this bill would most certainly bring about.

(d) Since it is impractical to place all information in the advertisement, some information must necessarily be omitted. For example, some drugs may be useful in treating a variety of diseases but the manufacturer may wish to call the physician's attention to the use of the drug in a single disease. We see no reason why he should not be permitted to do so. Similarly, most drugs have side effects or various types on various classes of patients, some of them extremely important and some of much less importance. They cannot all be listed in the advertisement in such a way as to convey their relative importance and significance to the medical reader except by a detailed discussion, similar to that included in the package insert or brochure, which would take up too much space in the advertisement. H.R 6471 makes no provision for this problem.

(e) Lastly, there is the problem of overlapping jurisdiction. The Food and Drug Administration already has full jurisdiction over the content of all information referred to in H.R. 6471 and sees that it is transmitted to physicians in appropriate forms. In view of the matters outlined in this statement no useful purpose would be served by also giving the Federal Trade Commission power to require that the same subjects be covered to its satisfaction in medical journal advertisements.

As I stated at the outset there is no disagreement between the Pharmaceutical Manufacturers Association and the proponents of H.R. 6471 concerning the importance of full disclosure to physicians. We do disagree, however, on the means by which advertisements should properly be required to achieve this purpose. I have attempted to set forth the Pharmaceutical Manufacturers Association's position in this statement. To resolve the problem and at the same time to assure that medical journal advertising refers the physician to the appropriate literature about side effects and contraindications we would suggest that the following amendment be made instead of the amendment set forth in H.R. 6471:

"*Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled*, That subsection (a) of section 15 of the Federal Trade Commission Act is amended (1) by striking out the period at the end of the last sentence of paragraph (1), and (2) by inserting in place thereof the following: "and, if it is an advertisement of a prescription drug, contains the following statement: 'Before prescribing be sure to consult the manufacturer's literature for information about possible side effects and contraindications'. For the purposes of this paragraph a prescription drug is one intended for use of man that Federal law requires to be dispensed only upon the prescription of a practitioner licensed by law to administer such drug".

We submit that the above amendment to the present section 15 would (a) adequately remind the physician that the advertisement of a prescription drug does not necessarily tell the full story of the product and refer him to the

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appropriate source of such story, (b) preserve the accepted character of prescription drug advertisements as essentially reminder pieces that present only salient facts, (c) allow the medical journals to continue their important role of providing the physicians with current scientific reports, (d) draw increased attention to and thereby further the full disclosure program of Food and Drug Administration and other groups, (e) preserve intact the traditional roles and functions of the Federal Trade Commission and the Food and Drug Administration, and (f) allow manufacturers and editors to make their advertising judgments with certainty as to the law's requirements.

[From the New York Times, Aug. 18, 1961]

ADVERTISING: DRUGS IN A CUTBACK

(By Peter Bart)

The drug industry has been going through some trying times in recent months. Senator Estes Kefauver, Democrat, of Tennessee, and other political figures have kept up a barrage of criticism directed against the pharmaceutical companies. And a bewildering variety of new rules and regulations have been adopted in an effort to correct alleged abuses by drugmakers.

Meanwhile, many drug producers have complained about a squeeze on their profits arising out of increased operating costs. And only yesterday antitrust charges were filed against three major companies Chas. Pfizer & Co., Inc., American Cyanamid Co. and Bristol-Myers Co.

As a result of all this, a number of leading drug producers have quietly been cutting back on advertising. The reductions have not been dramatic—but they have been heavy enough to hurt the vast medical press.

It was learned yesterday, for example, that Medical News, a weekly newspaper of the medical profession, had been forced to suspend publication mainly because of the drug companies' cut in advertising. Its staff of 21 persons was told yesterday of their dismissal.

STARTED IN 1955

Medical News started publication in 1955 under the sponsorship of a big drug producer, Ciba Pharmaceutical Products, Inc. Last year Ciba cut the publication loose and it has operated as an independent journal since then. Scope, another well-known medical magazine published by a leading drug company (Upjohn Co.) also was cut loose last year, and ceased publication.

An official of Medical News said yesterday: "We had sufficient capital to make a go of it. But the ads just weren't there." The newspaper, which was sent free to 150,000 practicing physicians, depended on advertisements for all of its revenue.

Several other leading publications aimed at doctors also are feeling the advertising pinch. A spokesman for Medical Tribune, the rival to Medical News in the weekly field, acknowledged that advertising was down in the first half of 1961.

An official of the Journal of the American Medical Association said his publication had carried significantly fewer advertisements so far this year than it had last year. The publisher of another medical publication, who keeps a tabulation of advertising linage in his field, said advertisements were down from 10 to 30 percent in medical magazines during the first half of 1961.

DIFFICULTIES ENCOUNTERED

One key reason for the reduction in advertising by major pharmaceutical companies stems from their increased difficulties in introducing new products. The Government has imposed a number of new rules providing for increased testing of new drugs both by the producers and by the Government. All this has slowed the flow of new drugs into the market.

Because drug companies have not been able to introduce as many new drugs as before, they therefore have not had to advertise them in medical publications.

At the same time, drug houses have had to divert some advertising funds into revising their overall promotion effort to meet new Government rules. The Merck, Sharpe & Dohme Division of Merck & Co., for example, is spending $250,000 to revise its promotional literature. These revisions were required by

Government regulations providing that all circulars sent to doctors contain so-called contraindications—hazards, side effects and precautions.

Drug companies in recent months have been buffeted by criticism of their high promotion expenditures—criticisms mainly generated by Senator Kefauver's investigation. Thus, by cutting back on advertising, the pharmaceutical companies not only save money but also can contend that they are doing so in the hope of bolstering their industry's public image.

MULTIMILLION MERCHANTS

Top radio advertising officials will receive an education in retailing next month at a series of management conferences sponsored by the Radio Advertising Bureau, Inc. The bureau has completed a study of the Nation's "multimillion-dollar merchants" and plans to detail its findings at the meetings. Officials who attend the conferences will be told of the basic business views held by top retailers. They also will hear about the basic problems faced by the merchants. Eight management conferences will be held between September 7 and October 13 in various cities.

STATEMENT OF PRINCIPLES OF ETHICAL DRUG PROMOTION (PASSED BY PHARMACEUTICAL MANUFACTURERS ASSOCIATION BOARD OF DIRECTORS ON MAY 24, 1958)

We, members of the Pharmaceutical Manufacturers Association, recognizing our responsibilities and obligations to promote the public welfare and to maintain honorable, fair, and friendly relations with the medical profession, with associated sciences, and with the public, do pledge ourselves to the following statement of principles:

(1) Prompt, complete, conservative and accurate information concerning therapeutic agents shall be made available to the medical profession.

(2) Any statement involved in product promotional communications must be supported by adequate and acceptable scientific evidence. Claims must not be stronger than such evidence warrants. Every effort must be made to avoid ambiguity and implied endorsements. Whenever market, statistical or background information or references to unpublished literature or observations are used in promotional literature, the source must be available to the physician upon request.

(3) Quotations from the medical literature or from the personal communications of clinical investigators in promotional communications must not change or distort the true meaning of the author.

(4) If it is necessary to include comparisons of drugs in promotional communications, such comparisons must be used only when they are constructive to the physician and made on a sound professional and factual basis. Trademarks are private property that can be used legally only by or with the consent of owners of trademarks.

(5) The release to the lay public of information on the clinical use of a new drug or to a new use of an established drug prior to adequate clinical acceptance and presentation to the medical profession is not in the best interests of the medical profession or the layman.

(6) All medical claims and assertions contained in promotional communications should have medical review prior to their release.

(7) Any violation of these principles brought to the attention of the president of the Pharmaceutical Manufacturers Association shall be referred by him to the board of directors.

ABBOTT LABORATORIES,
North Chicago, Ill., November 14, 1961.

HON. OREN HARRIS,
Chairman, Committee on Interstate and Foreign Commerce,
House of Representatives, Washington, D.C.

DEAR MR. CHAIRMAN: On behalf of Abbott Laboratories, I would like to present our position on H.R. 6471, 87th Congress, and to correct the record in certain respects.

First, Abbott Laboratories, as a member of the Pharmaceutical Manufacturers Association, fully subscribes to the statement submitted on September 21, 1961, by Theodore G. Klumpp on behalf of this association. For the reasons stated by Dr. Klumpp, we oppose H.R. 6471 in its present form as adverse to the public

interest. Since no purpose would be served in doing so, I will not repeat these reasons in this statement.

Second, of special interest to Abbott Laboratories, I would like to express our concern about certain misleading implications which appear in the record of the proceedings of this committee on H.R. 6471, particularly as they apply to us.

Specifically, we feel impelled to correct the record concerning the promotion and advertising of our diuretic drug Oretic, the generic name of which is hydrochlorothiazide. As the record stands now, the public might be misled into thinking that doctors have not had the opportunity of seeing our printed precautions on this drug. Such a conclusion would be totally false.

In his letter to the Honorable Oren Harris, chairman of the Committee on Interstate and Foreign Commerce, dated September 1, 1961, the Honorable Paul Rand Dixon, Chairman of the Federal Trade Commission, listed an advertisement for Oretic appearing in the October 22, 1960, issue of the Journal of the American Medical Association as an example of an advertisement of one full page not devoting any space to a discussion of side effects and contraindications, although the drug may produce side effects and there are certain contraindications to its use. The overall category within which Commissioner Dixon listed this drug was entitled as follows: "(A) Copies of Advertisements Which Illustrate the Failure To Deal Appropriately in Advertising With the Subject of Drug Side Effects and Contraindications." Speaking of this category, Commissioner Dixon stated "* * * only the pharmacist ordinarily would have the opportunity of seeing the manufacturer's printed warning of side effects and contraindications for his products that appear on the package inserts."

As applied to Oretic this is a completely misleading statement. Commissioner Dixon apparently failed to investigate our promotional activities in connection with Oretic. As is our general policy, in the case of Oretic we took great care to insure that physicians were fully informed as to the use of this drug, including side effects and contraindications.

Let me briefly recite what we did to inform the doctor about the advantages and precautions associated with the use of Oretic. This product was first marketed on July 2, 1959, some 15 months prior to the advertisement referred to by Commissioner Dixon.

Simultaneously with the marketing of Oretic, we published and distributed a 16-page physician's reference booklet on this product. The subjects covered by this booklet were chemical characteristics, metabolic effects, indications, dosage and administration, how supplied, precautions and side effects, clinical studies, pharmacology, and references. There are two full pages under the heading "Precautions and Side Effects," and in addition precautions are also discussed in other sections of the booklet. This booklet was approved by our medical department and reviewed by the Food and Drug Administration. We are satisfied that it contains a thorough discussion of the proper use of Oretic.

We have distributed approximately 120,000 (as of October 16, 1961) copies of this booklet. The method of distribution was as follows: On July 2, 1959, we sent approximately 80,000 copies to our salesmen for personal delivery to physicians in connection with routine calls made by the salesmen. The balance was distributed in response to requests for additional copies or requests made directly to the company. A copy of our Oretic physician's reference booklet is attached to this statement and marked "Exhibit A."

In addition, we printed and distributed 156,000 copies of a product file card on Oretic. These were distributed at the time of announcement of the drug by direct mail to pharmacists and through our salesmen to doctors. When our supply was depleated, we reprinted approximately 38,000 additional copies of our file card. This card contained abbreviated information about Oretic and, also, in heavy print, an instruction to ask an Abbott representative for a copy of the Oretic physician's literature containing a complete guide to administration and dosage, clinical and pharmacological data, and important precautionary information.

We also sent each salesman a 16-page Oretic portfolio prepared for the purpose of aiding the salesman in his discussion of the product with the doctor. This portfolio included a detailed statement of side effects and precautions in the use of Oretic.

On June 29, 1959, we mailed over 100,000 sample packages of Oretic to our salesmen for personal delivery to doctors. Each sample package contained a printed insert with six panels of written matter, including precautions, plus a notice to the doctor to consult complete precautionary information in Oretic

professional reference literature. Additional sample packages were mailed to salesmen on request.

On July 25, 1959, our first journal advertisement for Oretic appeared in the Journal of the American Medical Association, with a circulation of 178,000 doctors. This was not an ordinary ad. It contained eight full pages, including a complete statement of precautions and side effects. The ad was in the form of an insert which could be detached by the physician and retained for future reference. In order to insure complete coverage of all physicians, we sent on September 18, 1959, to approximately 106,000 physicians by direct mail a copy of the 8-page folder which had previously appeared in the Journal of the American Medical Association. A copy of this folder is attached to this statement and marked "Exhibit B."

In our opinion, the activities described above enabled us to provide information concerning Oretic, including appropriate precautionary information, to all physicians who would be likely to prescribe Oretic, including general practitioners, internists, and selected specialists.

From time to time, of course, Abbott engaged in promotional activities, both by way of direct mail and in journal advertising, designed to remind the physician about the product. Among these activities was the placing of the advertisment referred to by Commissioner Dixon in his letter. The purpose of this advertisement was certainly not to educate the physician about the proper use of Oretic. It was not intended to be a catalog of indications, dosage, clinical studies, chemistry, pharmacology, or precautions and side effects. This could not be done on a single printed page, and an attempt to do so might very well mislead the physician as stated by the American Medical Association in its letter to the committee dated August 10, 1961, to assume that he might safely prescribe drugs solely on the basis of Journal advertisements. Rather, the purpose of the ad was to attract and remind the physician about Oretic. This was done by attempting to show that the "saluretic" effect of Oretic permits a more liberal low-sodium diet. In other words, a hypertensive patient on this drug can have some salt in his food. A copy of our advertisement, which appeared in the October 22, 1960, issue of the Journal of the American Medical Association, is attached to this statement and marked "Exhibit C."

It is inconceivable to us that a physician would undertake to prescribe Oretic solely on the basis of this type of advertisement. If we could not engage in reminder advertising of this nature, this would be tantamount to a legal prohibition against advertising, a strange thought in our free enterprise economy. After all, there is a limit to the number of times we can send a complete product brochure to the physician.

The position taken by Commissioner Dixon in his letter ignores the many ways in which physicians actually are informed about the drugs which they prescribe. For example, in the 1960 edition of the reference work entitled "Physicians' Desk Reference" there appears on Page 609 a brief summary statement of the composition, action and uses, administration and dosage, precautions, and other information on Oretic. Furthermore, there is a notice advising the physician to see product literature for complete precautionary information. Moreover, the generic drug was evaluated by the council on drugs, and this evaluation was published in the January 16, 1960, issue of the Journal of the American Medical Association. The generic drug also is described in the 1961 edition of the work "New and Nonofficial Drugs," published by the Council on Drugs of the American Medical Association. A brief summary of the council's opinion also appears in the July 8, 1961, issue of the Journal of the American Medical Association.

It should be pointed out that Oretic is Abbott's trade name for the generic drug hydrochlorothiazide. Hydrochlorothiazide is a member of a class of drugs generally referred to as "thiazides." The first thiazide diuretic was introduced by Merck & Co. in November 1957. This drug is called chlorothiazide, and is marketed under the trade name Diuril. Hydrochlorothiazide is a derivative of chlorothiazide, and was first marketed by Merck & Co under the trade name Hydrodiuril and by Ciba Pharmaceutical Products, Inc., under the trade name Esidrix in February 1959. Actually, Abbott Laboratories was the third company to market the drug hydrochlorothiazide. When announced by Abbott in July 1959, the medical profession had already been familiar with this drug for 5 months and with the thiazide family for nearly 2 years.

As a matter of fact, we have had occasion to check the medical literature for published clinical reports made by physicians on both chlorothiazide and hydrochlorothiazide for the period January 1957 to September 1960. We have dis-

covered a voluminous number of reports, a list of which is enclosed with this statement, as exhibit D. Thus, the physician is not obliged to rely upon promotional activities of manufacturers to gain adequate information on the proper use of new drugs. Not only are there numerous reports published in the literature, but physicians also attend medical meetings where they receive firsthand information on new developments in therapeutics.

H.R. 6471 would amend the Federal Trade Commission Act so as to require that all advertisements of prescription drugs contain a conspicuous and truthful disclosure of (i) the quantitative formula of the drug with each active ingredient listed by its common or usual name, (ii) the side effects of the drug, and (iii) the contraindications of the drug. Commissioner Dixon recommended in his testimony given on August 2, 1961, that the bill be amended by requiring, also, the disclosure of the efficacy of the drug. In addition, H.R. 6471 directs the Federal Trade Commission to prescribe such rules and regulations as may be necessary to administer these provisions. The effect of these proposals would clearly be to radically change the function of advertising as we know it today.

Regulations issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act currently require that the labeling of prescription drugs contain adequate directions for the use of such drugs by physicians. In essence, H.R. 6471 places all advertising in the same category as labeling. To confuse the functions of labeling and advertising in this manner is actually to destroy the important function of advertising to remind and to attract. Congress should not interfere with the operation of our free economy so drastically as this on the basis of such meager and misleading evidence as has been presented.

We would have no objection, however, to a statutory requirement to include a statement in advertisements directed to physicians indicating that the physician should consult the manufacturer's literature for a full statement concerning the proper use of the drug.

We should like to conclude by reminding the committee that any legislation which it might propose should take into consideration the full story with respect to the way in which drugs are currently marketed, including the requirements of existing law. If advertising is truthful, it serves a valid function in the American society for the drug industry as well as for other industries. The Federal Trade Commission Act is not a proper vehicle in and of itself to prescribe the information which should be given to physicians.

We submit that the combination of the labeling requirements contained in the Federal Food, Drug, and Cosmetic Act, the self-interest of manufacturers acting competitively, and the exercise of responsibility by the medical profession itself, are adequate to protect the public health and insure the dissemination of full information to physicians, an objective which we heartily endorse.

We hereby request that this letter be made a part of the record of the proceedings on H.R. 6471.

Respectfully submitted.

PAUL GERDEN, *Vice President.*

Mr. SCHENCK. Mr. Chairman, if you will yield to me, as I recall, we had only a very short hearing on this bill sponsored by our colleague, Mr. Dingell, I think less than one morning of hearings.

The chairman of our subcommittee was unavoidably away from Washington and you personally presided and adjourned the hearing subject to the call of the Chair.

So, for that reason, I think the hearings have not been printed.

Mr. DINGELL. For the record, Mr. Chairman, may I say that I level no criticism whatsoever at that committee. As a matter of fact, since I was aware of the fact that this other bill was coming, I made no effort, since I thought the committee would not take further action, as we had this other measure, in which I had hoped, and it happily worked out, that the provisions were included here, so I hope this will not be taken as being either critical of the Chair or the committee, and I am appreciative of the courtesy of the Chair in holding the hearings, and, in my opinion, it has worked out better.

Mr. SCHENCK. Mr. Chairman, all I want to point out is that those hearings were not completed, and, for that reason, the hearings were not printed.

The CHAIRMAN. The Chair is always glad to accommodate members of the committee and others, when he can.

Mr. Cain, thank you very much for your presentation here this evening.

Mr. CAIN. Mr. Chairman and gentlemen, thank you.

The CHAIRMAN. Mr. Lyman C. Duncan?

Mr. Duncan, we will be glad to have your statement.

STATEMENT OF LYMAN C. DUNCAN, ON BEHALF OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION, ACCOMPANIED BY LLOYD CUTLER, ESQ.

Mr. DUNCAN. My name is Lyman C. Duncan. I am a vice president of American Cyanamid Co. with primary responsibility for two of its operating divisions, one of which is Lederle Laboratories, a manufacturer of antibiotics, biologicals and pharmaceuticals for more than half a century.

I appear before you as one of the witnesses on behalf of the Pharmaceutical Manufacturers Association. My comments will be confined to section 107, entitled "Biological Drugs," of H.R. 11581.

Biological drugs for human use include the various vaccines, sera, toxoids and so forth which are essential for the protection of man against the scourge of certain epidemic diseases for which no effective treatment has ever been devised. Such products have been subject to strict licensing controls on the part of the Federal Government since July 1, 1902. The licensing jurisdiction is vested in the Public Health Service by the Public Health Service Act of July 1, 1944.

Section 351 of that act forbids the sale, interstate shipment, export or import of any virus, therapeutic serum, toxin, antitoxin or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man unless the product has been manufactured at an establishment licensed by the Secretary of Health, Education, and Welfare to manufacture it.

Licenses for the maintenance of establishments for the manufacture of such products are issued only upon a showing that the establishment and the product itself meet standards "designed to insure the continued safety, purity, and potency" of the product, as prescribed in regulations.

Licenses for new products may be issue only upon a showing that they meet such standards. The Secretary is given specific authority to prescribe regulations for the issuance, suspension and revocation of all such licenses.

In addition to this licensing control over establishments and products to insure safety, purity, and potency, which is administered by the Public Health Service, biological products for human use are also subject to the adulteration and misbranding provisions of the Federal Food, Drug and Cosmetic Act, administered by the Food and Drug Administration. Indeed, the provisions of that act apply generally to human biologicals, except for section 505, the new drug section.

Section 107 of H.R. 11581 would basically do three things:

First, it would amend section 351(d) of the Public Health Service Act to require, in addition to the present showing of "safety, purity, and potency," a further showing that biological products are also "efficacious under the conditions prescribed, recommended, or suggested by the manufacturer," before licenses may be issued.

Second, the bill also would add a new paragraph (e) to section 501 of the Federal Food, Drug, and Cosmetic Act, under which a human biological would be deemed to be adulterated if it was not prepared in conformity with the Public Health Service Act and the regulations and standards thereunder by a licensed manufacturer and in accordance with such license, or if at any time(1) it is not in conformity with the Public Health Service Act or regulations or standards thereunder, or (2) the expiration date on its labeling has passed, or (3) the license has been suspended or revoked.

Third, the bill would add a new paragraph (n) to section 502 of the Federal Food, Drug, and Cosmetic Act by which a human biological product would be deemed to be misbranded if its packaging or labeling is not in conformity with the Public Health Service Act or with the regulations or standards thereunder.

We are opposed to these provisions of section 107 of H.R. 11581 as unnecessary and unwise and because we believe that a thorough study is required of the many complexities involved in biologicals and their regulation before any changes are made in existing law. There is time for such a study and it should be made.

In the case of biological products, the public already has the protection that this bill proposes for new drugs. The public has this protection by virtue of the strict licensing requirements, per plant and per product, that biological products for human use be shown to be safe, pure, and potent. What problems exist in the regulation of human biologicals are problems of possible overregulation, not underregulation—that is to say, whether the present regulatory system, involving as it does licensing by the Public Health Service and overlapping jurisdiction by the Food and Drug Administration, is overly complex and unduly impedes the development of new biological products needed for the protection of man against disease and infection.

The proposed amendment of section 351(d) of the Public Health Service Act, which would introduce the same concept of efficacy into biological products as section 102 of the bill proposes for new drugs, is unnecessary. Section 351(d) presently requires a showing of "safety, purity, and potency." It is difficult to see what would be served by adding efficacy to those requirements, and confusion is the likely result.

You have heard Dr. Klumpp discuss the problems involved in applying the concept of efficacy to new drugs and the need for appropriate safeguards if the concept is written into the new drug provision. The problem is drastically more difficult in the case of biological products for various reasons.

Biologicals are generally used for the prevention, rather than the treatment of disease. Therefore, you cannot show "effectiveness" by physical results, such as a reduction in fever, or a bettering or worsening of the patient's condition. Instead, the demonstration of "effectiveness" must be largely statistical or else a showing that antibodies

are produced in sufficient quantities to give a reasonable level of immunity. A statistical showing presents problems because of variations in the incidence of a disease and the extent of its severity. For example, clinical tests have demonstrated that following an influenza immunization program, the incidence of flu may be reduced by one-half.

Other tests may demonstrate the incidence to be higher or lower. Who can say, under such circumstances, how "effective" flu vaccine is? After all the years it has been used, the "effectiveness" of flu vaccine is still controversial, yet no one can question the desirability of having the product available for use in the interests of the public health.

Additional problems arise because of variations in individual response and exposure. It is well known that biological immunizing agents are not completely effective because different individuals do not respond in the same way or to the same degree to vaccines, toxoids, sera, and the like. In addition, natural exposure may be sufficiently severe to overwhelm a reasonable level of immunity.

The need to meet emergency situations must also be kept in mind. In such situations manufacturers and the regulatory agency must be able to provide products which may be effective but for which there has not been time to permit thorough clinical study of the degree of effectiveness.

A good example is the experience in 1957 with vaccine for Asian flu. That vaccine had to be produced in tremendous quantities and marketed without evidence that it protected humans against the natural disease, but simply on the basis that it produced specific antibodies in humans.

What I have said only briefly illustrates the need for maintaining flexibility in judging the value of these biological products. Such flexibility must not be compromised by adding a nebulous requirement of "efficacy."

We submit that the existing law, which requires a showing of "potency," adequately meets the needs which the draftsman of H.R. 11581 apparently thought were desirable for the protection of the public against ineffective products.

PMA also opposes the provisions of section 107 of the bill which would deem biological products which do not conform to the requirements of the Public Health Service Act to be adulterated and misbranded under the Federal Food, Drug, and Cosmetic Act. We oppose these provisions as unnecessary because the Public Health Service Act prescribes penalties for violation of its requirements and gives to the Secretary adequate authority to suspend or revoke licenses.

Also, the creation of these additional sanctions under a different act, for violation of the Public Health Service Act, will unavoidably create confusion, particularly since they are inconsistent in various respects with the Public Health Service Act and appear to be based on incorrect presuppositions concerning practices followed under that act.

For example, proposed section 501(e) would deem a biological to be adulterated if at any time the license under which it was manufactured is suspended or revoked. That is inconsistent with the last sentence of section 351(a) of the Public Health Service Act which permits the sale by a person other than the licensee after a license

has been suspended or revoked unless the Secretary gives notice to the contrary.

The proposed adulteration section also is too broad and goes too far, because a license can be revoked or suspended for reasons having nothing at all to do with the safety, purity, or potency of the product. The regulations under section 351 of the Public Health Service Act provide for the revocation of a license if the manufacture of the product is discontinued. Thus, the proposed section 501(e) of the Federal Food, Drug, and Cosmetic Act would have the absurd effect of deeming a product, which was manufactured in accordance with an effective license, to be adulterated if at any subsequent time the licensee simply discontinues further manufacture.

In view of the foregoing comments, the transitional provisions of section 108 of H.R. 11581, which provides when and how the amendments proposed in section 107 will take effect, should be eliminated as unnecessary. In addition, section 108(d), which would permit revocation of existing licenses upon a finding by the Secretary that "there is substantial doubt as to whether such product is efficacious," is objectionable for the reasons heretofore given by Dr. Klumpp in commenting on section 104(b) of the bill which would permit the suspension of effective new drug applications on a finding of "substantial doubt" as to safety or efficacy.

Section 107 of H.R. 11581 would make drastic changes in the law presently governing biological drugs. We oppose them for the reasons I have stated and because we believe that such changes, or any changes, should be made only after a thorough consideration and review by this committee. They should not be made as a result of a few days of hearings.

They should be the subject of intensive consideration of the need for them and of the possible effects which they would have on the availability of biological products. We believe that the field of biological drug regulation needs such a careful study before any legislative change is made.

If such a study is made, we suggest it should focus on two main issues: first, whether the requirements of present law unduly impede the availability of new biologicals to the public, and second, whether the dual regulatory system, involving both the Public Health Service and the Food and Drug Administration, should be continued.

The points which may be considered under those issues include such questions as: (1) Is there at this time any justification or need for continuing strict licensing control over biological products for human use? (2) Would it be desirable to control these products in a manner similar to that used to control new drugs? (3) Should the availability of a new biological product be contingent upon the necessity of the adoption of detailed specific regulations relating to such product, or do such regulations for controlling the manufacture of such product act as a deterrent to innovation and as a premium or mediocrity? (4) Does the present dual regulatory system result in needless administrative confusion and hiatus? (5) Should time limits be imposed for acting on applications for licenses? (6) Should regulations for the issuance, suspension and revocation of licenses for biological products be made specifically subject to requirements for a hearing and judicial review such as provided in section 701 of the Federal Food, Drug, and Cosmetic Act?

We sincerely urge that a careful review of these and other questions involved in the complex field of biological drug regulation be made before any legislation is enacted, and we believe that, pending such review, the adoption of piecemeal legislation as proposed in section 107 of H.R. 11581 would be extremely unwise.

(The biographical sketch relating to Lyman C. Duncan follows:)

LYMAN C. DUNCAN

Lyman C. Duncan, vice president of American Cyanamid Co., with primary responsibility for its medical affairs, has been connected with the pharmaceutical and chemical industry throughout most of his business career.

He was named general manager of Cyanamid's Lederle Laboratories Division in April 1955, and assumed his present duties in November 1960.

Mr. Duncan joined Cyanamid in 1945 as manager of the procedures department in the company's head office. In 1950, he was named manager of the priorities and allocations department and, in 1951, assistant to the president.

From April 1953 until December 1953, he served as general manager of the Petrochemicals Division, and from then until his appointment to head Lederle, he was general manager of the Organic Chemicals Division.

Mr. Duncan was born in Flat Rock, Ill., in 1910. He graduated from DePauw University in 1932 and, 2 years later, obtained a master's degree in economics from the London (England) School of Economics.

Following his graduation, he was with the Ohio Oil Co. until 1937 and an associate editor of Barron's, business and financial weekly magazine, until 1941, when he was called to active duty with the U.S. Army.

During the war, Mr. Duncan served in various administrative posts with the Chemical Corps, rising from second lieutenant to lieutenant colonel. He was discharged in October 1945.

The CHAIRMAN. Does that conclude your statement, Mr. Duncan?

Mr. DUNCAN. That concludes my statement; yes, sir.

The CHAIRMAN. It is pretty difficult for me to rationalize your statement on page 1 with your final statement.

A biological drug, I understood you to say, is a drug for human use in an effort to curtail certain diseases for which there have been no known drug treatment. Is that right?

Mr. DUNCAN. Yes.

Now, what I was trying to say was this, very briefly: That, as medical knowledge has advanced, we developed a whole series of drugs that will treat a great many of the bacterial diseases.

Now, as we narrow down the field, we still have the whole field of viruses where there is no effective drug treatment.

Antibiotics generally will not treat viral diseases. Neither will drugs we have discovered so far. So we, therefore, continue to protect the public against viral diseases by vaccination, by live and modified live and killed viruses which stimulate the development of antibodies in human beings.

I tried to make the point of distinction here as between the treatment of a disease and the attempt to prevent a disease.

The CHAIRMAN. Are you trying to say, then, that these vaccines, toxoids, and so forth, should be dispensed promiscuously?

Mr. DUNCAN. Oh, no.

The CHAIRMAN. I gather from your statement about the study that you thought ought to be made that you indicated that there was some doubt as to whether they should be subject to regulation at all.

Mr. DUNCAN. No. I really said this:

The biologicals are controlled by the Public Health Service Act. It is an act that has different provisions than the Food and Drug Act.

The last time that act was revised, I believe, was in 1944. I am not being critical.

I am just suggesting that before any changes are made, a study should be made of that act, because it is so different from the Food and Drug Act.

As things stand at the moment, the biologicals are controlled by the Public Health Service Act.

Now, technically, there is some overlapping, as I pointed out, because the Food, Drug, and Cosmetic Act also applies to biologicals as medication.

But, in practice, I think, by precedent and general agreement, the biologicals are controlled under the Public Health Service Act by Administrators in the Surgeon General's Office, whereas, of course, the Food and Drug Administration controls the administration of drugs

Now, I have said that, in effect——

The CHAIRMAN. This series of questions you raised should be studied, then, to determine whether it should be controlled under one procedure or another?

Mr. DUNCAN. Exactly; yes, sir.

The CHAIRMAN. All right.

Mr. Schenck?

Mr. SCHENCK. The only question I have to ask Mr. Duncan is that these are all prescription drugs, are they not?

Mr. DUNCAN. They are; yes, sir.

Mr. SCHENCK. All the biologicals and the rest of them?

Mr. DUNCAN. I am positive they are, yes.

The CHAIRMAN. Mr. Dingell?

Mr. DINGELL. No questions, Mr. Chairman.

A very excellent statement, sir.

The CHAIRMAN. Thank you so much.

Dr Raymond A. Bauer.

Dr. Bauer, you may proceed.

STATEMENT OF RAYMOND A. BAUER, PROFESSOR AT HARVARD GRADUATE SCHOOL OF BUSINESS ADMINISTRATION, ACCOMPANIED BY PROF. MARK G. FIELD, BOSTON UNIVERSITY, AND LLOYD CUTLER, ESQ.

Mr. BAUER. I am Raymond A. Bauer, professor at the Harvard Graduate School of Business Administration. My professional field is social psychology. I have been a consultant to the pharmaceutical industry, chiefly on problems of marketing and marketing research. I have published many papers in the area of social communications.

For a considerable number of years I did research and directed research in the field of Soviet studies, and am the author or coauthor of a number of books and many articles in this area. During the past several months I have done certain research on problems of the pharmaceutical industry. This research has been done in connection with Arthur D. Little, Inc., for the counsel of the Pharmaceutical Manufacturers Association.

One of these studies is a survey of certain contrasting problems of the American and Soviet pharmaceutical industries.

Copies of the full report, that is this document, have been submitted and I respectfully request that it be inserted into the record.

(See p. 344 for the information mentioned.)

In this study, my colaborator has been Professor Mark G. Field, formerly associate professor of sociology at the University of Illinois, who has just recently joined the faculty of Boston University. Professor Field is an authority on the sociology of Soviet medicine. He has published a book and numerous articles on Soviet medicine including the Soviet pharmaceutical system, and is presently working on a book on the organization of Soviet medicine.

Professor Field is present and will be available to answer questions on points on which he is better qualified than I am.

This study, presenting such a different way of looking at the American pharmaceutical system, illuminate certain social benefits of the American system that get overlooked in much of today's discussion. Briefly stated, the Soviet study reemphasizes in somewhat novel perspective the following social benefits of our system of drug production and distribution: getting drugs to the doctor and patient with minimal delay, assurance of good quality, and assurance of adequate quantities of drugs.

A close scrutiny of the Soviet drug system may well provide a meaningful comparison to our own system and allow us to gain some new insights into our own problems. It is indeed characteristic of any reasonably complex institutional arrangement that it has both advantages and disadvantages. The question is how to maximize the former and minimize the latter.

The lessons of the Soviet scene are intriguing. We have found in both socialist Russia and socialist Czechoslovakia strong complaints over the high prices of drugs, and this in supposedly noncommercial socialist economies. The Soviet system features very conservative promotion of drugs in contrast to our elaborate—and it is contended, sometimes, expensive—methods of promoting ethical pharmaceuticals to the doctor. Quality control of Soviet drugs primarily lies with an independent government inspection system, rather than with the manufacturer. There is no so-called needless duplication of research facilities. Research is done in independent centralized research institutes. Factories are allocated quotas of drugs to produce, for which they receive an assigned "reasonable" profit.

In a word, the Soviet situation seems to approximate the ideal institutional arrangement impiled in many criticisms of our own industry. What are the results?

The Soviet medical press contains repeated complaints over the inadequacies of the promotional system. Doctors are said not to be up-to-date in their knowledge of new drugs, with the result that treatment of patients suffers, and druggists spend needless time compounding drugs which are available in prepared form. Pharmacists are urged to go to the doctors and "detail" them on new drugs, and pharmacists who do so are praised in the press. Official sources advocate advertising drugs via newspapers, radio, and television.

The Soviet medical press also features apparently characteristic instances of batches of drugs of very poor quality caught by the inspection system. At present, active steps are being taken to build quality control into the manufacturing process, and to make it the

responsibility of the firm which produces the product, rather than of the independent inspection system. In other areas of the Soviet economy, we know that this attempt to build quality into the production process has been accompanied by the open espousing of advertised trademarks which will enable the consumer to favor those factories in whose products he has confidence. This process has not so far been extended to the Soviet pharmaceutical industry, but the basic logic of the situation seems to be identical.

I mentioned the fact that the Soviet economy is spared the expense of duplication of research facilities, as compared with this country where every major firm has its own laboratory setup. While there may be certain savings in the development of laboratory products, Soviet sources indicate that a price is paid with long delays in getting products into production because of poor communication between the research institutes and the producing facilities. Delays of 2 to 3 years are cited as typical.

Finally, there are the typical selective shortages which characterize the Soviet economy. While exotic drugs may be in good supply, there may at the same time be shortages of such prosaic items as surgical cotton or boric acid. This has to do with the fact that there is a form of profit system within the socialized economy. Prices are set for the products which a factory is assigned to produce. For reasons which the pricesetter can never fully anticipate, some products are always more profitable than others. This produces the perennial Soviet problem of the "product mix"; the factory produces that assortment of products that optimize its financial picture. The correspondence between this product mix and the planned assortment is usually imperfect.

These several characteristics of the Soviet pharmaceutical system are not a series of isolated features. They represent a systematic contrast with our own system based on brand names, and promotion not only of individual products, but of a company's range of products. It is quite likely that each system can be improved within its own prescribed framework. However, I will say this: the Soviet evidence certainly gives added plausibility to the American brand name manufacturers' defense of his own position.

Let us look back on this picture for a moment from the point of view of the American brand name manufacturer. When pressed on the profitability of individual items in his line, he typically protests that he should not be judged on the basis of individual items. Profitable items, he argues, support other unprofitable drugs which he develops and markets for the convenience of the medical profession and the welfare of patients, often with rare diseases. He will go further and state that his policy is to promote his line across the board. By identifying himself with a line of drugs, he creates confidence in the doctor in his firm and his line of drugs. Part of the cost of promotion must be assigned to establishing this identification. This, in turn, motivates the firm to maintain quality, and to produce a less profitable item. Thus, while there are characteristic costs associated with the brand name promotion of ethical drugs, the defense would contend that these costs are intimately tied to the benefits: drugs rapidly distributed and produced, informed doctors, high quality, adequate quantities.

The CHAIRMAN. I see no objection to having it included in the record, although I am not too sure, Doctor, just how much it is going to contribute to consideration of this legislation. I think the general information seems to be a very good thing to have, so let it be included in the record.

(The information referred to follows:)

THE SOVIET AND THE AMERICAN PHARMACEUTICAL SYSTEMS: SOME PARADOXICAL CONTRASTS

(By Raymond A. Bauer and Mark G. Field)

In a speech delivered before the Supreme Soviet of the U.S.S.R. in February 1957, Maria D. Kovrigina, then Health Minister of the Soviet Union, complained bitterly about the retail prices of drugs in the U.S.S.R. Pointing out that over the previous 5 years the unit cost of production in the medical industry had been more than halved (the wholesale prices, for example, of crystallic penicillin had been reduced more than ninefold and of streptomycin more than thirtyfold), she wondered why this did not lead to a corresponding decrease in the retail prices of Soviet pharmaceuticals. Unfortunately this is not the case, concluded Madam Kovrigina: "the prices of some highly effective preparations are four, five, and even six times the wholesale prices. Reducing retail prices of medicines * * * is a very important step. We have made such a proposal to the U.S.S.R. Council of Ministers and we expect our request to be met".[1]

A similar difficulty exists in another Iron Curtain country. A European representative of an American drug firm has become friendly over the years with a highly placed person in Czechoslovakia's state health establishment. This friend exhibited interest in the senatorial investigation of the American pharmaceutical industry, and asked for some of the material from these hearings. "I don't want the full text," he noted, "just the rebuttal material used by your American manufacturers. They say our drug prices in Czechoslovakia are too high."[2]

These complaints have a strikingly familiar ring. In the past few years, the American pharmaceutical industry has been subjected to a great deal of criticism along a similar vein. Specifically, it is charged that:

(1) There is too great a discrepancy between production costs and retail prices of pharmaceuticals.

(2) The research done by ethical drug companies is not only wasteful, because of unnecessary duplication of facilities, but also it is trivial, since it is done mainly for competitive and commercial purposes.

The specifics of the first charge arise from puzzlement as to why advertising and other promotional costs are so high for ethical pharmaceuticals compared to similar costs in other industries. And there is little doubt that these costs are relatively high. According to various estimates, the promotion of ethical drugs amounts to around 20 percent of the manufacturer's price to the wholesaler. This expense supports a large volume of journal and direct mail advertising, and a corps of missionary detailmen whose functions are distinctive to the drug industry. In major drug firms, several hundred or more detailmen may be assigned the duty of informing doctors of their companies' products, and hopefully to persuade them to prescribe the particular products, usually brand named, produced by their firms.

Critics of the American pharmaceutical industry see little justification for price differences between these branded drugs and the unbranded "generic" drugs which are chemically identical in their main ingredients, and which usually are not promoted in any substantial way, and generally sell for less at the manufacturer's level. Regarding the expense of promoting branded drugs as especially unwarranted, the more extreme of these critics argue for reducing promotional activity to some minimum system of announcements of new drugs, with the major job of communicating the drug's characteristics and usefulness to be performed by the medical profession or the government, or both. Brand names, presumably, would be done away with, or become for all practical purposes irrelevant. In short, the first charge is that American ethical pharma-

[1] Speech by Deputy M. D. Kvorig[illegible], Izvestia, Feb. 8, 1957, p. 5.
[2] Told by Walter A. Munns, pr[illegible] of Smith Kline & French Laboratories in a speech before the New York Security Analysts, Inc., New York, Jan. 9, 1962.

ceuticals are overpromoted, and that this overpromotion imposes an unreasonable and unwarranted cost to the public.

A second accusation leveled against the American drug industry concerns the use of commercial research facilities. The cornerstone of this argument is that the major discoveries on which American advances in pharmaceuticals have been based, originated mainly in Government or university laboratories, and not in the drug companies' laboratories. The contention is that certain unprofitable areas (cancer, for example) suffer neglect as a consequence of American pharmaceutical companies' interest in lucrative new drugs. It is further asserted that the secrecy attached to competitive commercial research actually inhibits the rate of discovery of fundamentally new drugs. These critics' conclusion is that as good or better research could be done more economically in independent, noncompetitive laboratories, preferably located in universities or Government institutions.

How valid are these charges? How can we appraise their accuracy? One interesting way is to take a close look at the Soviet system where conditions tend to be just the reverse of those in America. For example, in Soviet Russia drugs tend to be underpromoted and pharmaceutical research is conducted, not by individual drug firms, but entirely by Government-sponsored "institutes." This is why the complaints about retail drug prices and ineffective research in the U.S.S.R. are especially surprising, since the methods employed by the U.S.S.R. for "promoting" and researching new drugs largely parallel those advocated by some critics of the present American system.

In a sense, the Soviet Union, with its governmentally operated and financed, centrally administered, and planned pharmaceutical system, provides us with a readymade experiment on the effectiveness of an alternative method for providing pharmaceuticals to the population of a large-scale industrialized society. A close scrutiny of the Soviet drug system, then, may well provide a meaningful comparison to our own system and allow us to gain some new insights into our own problems. It is indeed characteristic of any reasonably complex institutional arrangement that it has both advantages and disadvantages. The question is how to maximize the former and minimize the latter.

Let us also state at the outset that we have no intention of raising the wornout specter of "socialized medicine," or of socialism, in general. Moreover, since some of what we have to say will seem to be critical of the Soviet medical system, we hasten to say that this is not our intention. All-in-all, we feel that the achievements of Soviet medicine are considerable.[3]

Nor is the quality of Soviet medicine entirely inferior to that in the United States. Admittedly Soviet doctors, for the most part, must content themselves with patently inferior equipment and supplies, but their effectiveness, as testified to by personal experience, and by the opinions of Soviet refugees (in most other respects critical of the Soviet system in general), is considerable.[4]

Informed observers have pointed to certain superiorities of American medical training, but here again the differences are one of degree and there is no reason to categorize Soviet medical training as generally poor.[5]

The supply of doctors in the U.S.S.R. exceeds that of the United States even on a per capita basis. Only Israel does better. There are presently over 400,000 physicians in the Soviet Union; in fact, 1 in every 4 physicians in the world today is a Soviet doctor. In the Soviet Union the ratio of doctors to 10,000 of the population is now 18, whereas the corresponding proportion in the United States in 1955 was 13.2 and declining. As a result, we must import foreign-trained physicians while the Soviet Union will soon be in the position of exporting some of its doctors.

Rather than make general evaluations of the two medical systems, in this article, we are concerned with what might be termed the "comparative institutional approach." We will examine certain specific institutional arrangements and practices that could, if we so desired, be introduced into our mixed economy without moving us along the road to socialism. We shall attempt, as far as

[3] Cf. Field, Mark G., "Medicine in Soviet Land: Its Realities and Challenge," Modern Medicine, vol. 27, No. 14, July 15, 1959, pp. 196–207, and Field, Mark G., "Health Services in the U.S.S.R.," Soviet Survey, No. 35, January-March 1961, pp. 100–105.

[4] Cf. Field, Mark G., "Doctor and Patient in Soviet Russia" (Cambridge: Harvard University Press, 1957) pt. III, pp. 183–220; also "Former Soviet Citizens' Attitudes Toward the Soviet, the German, and the American Medical Systems," American Sociological Review, 20 (December 1955) pp. 674–679.

[5] Cf. The report of the U.S. public health mission to the Union of Soviet Socialist Republics, U.S. Department of Health, Education, and Welfare, Washington, D.C., 1957.

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possible. to look upon these arrangements as being analytically distinct from certain features peculiar to Soviet society and the Soviet economy. Empirically, of course, such a separation cannot often be made.

We also feel it is quite significant that the Soviet health authorities themselves are searching for, and to some extent stumbling upon alternatives of their own without abandoning either socialism or socialized medicine. Many of these solutions have a distinctly "capitalistic" flavor. There is little doubt, furthermore, that on the Soviet as on the United States medical scene, the pharmaceutical question is an important and as yet unsatisfactorily resolved problem. In a recent review of the pharmaceutical situation, it was said:" * * * if one follows the medical press carefully over a period of time, the single most important cause of complaints is the poor work of the pharmaceutical industry and (to about the same degree) of the medical instruments industry".[6]

"UNDERPROMOTED" DRUGS

One major criticism of the American ethical drug industry centers, as we have seen, around the high costs of promoting drugs, together with the practice of maintaining brand names and brand lines. The assumptions behind this criticism are more complex than generally recognized, and seem to imply the following propositions:

(1) An adequate noncommercial source of information about drugs can be established without too much difficulty.

(2) If information is reasonably available, physicians will take the initiative to see that they are kept up to date.

(3) The well-informed physician will not be concerned with the reputation of the firm producing the drug, but only with the drug's properties as described in an official pharmacopoeia.

(4) Adequate quality can be insured at reasonable cost by a Government inspection system.

(5) An adequate supply of pharmaceuticals will be produced if reasonable profits are allowed on individual drugs. (This final asumption which at first glance seems remote is a counter to the contention of American industry spokesmen that high profits on some drugs make it possible to maintain a relatively full line, including some medically critical but less profitable items.)

One way of finding out whether these propositions are likely to prove true or false is to see whether they hold true in the Soviet system where drugs are not promoted. Before we do so, however, it might be wise to describe the characteristics of the Soviet pharmaceutical system. If, like the Soviet medical system as a whole, is characterized by extreme centralization and bureaucratization and by the existence of rigidities and slowness in action which, so often, go with advanced bureaucracy. Having overall responsibility for the pharmaceutical system of the Soviet Union are two specialized organizations within the U.S.S.R. Health Ministry. The Pharmacological Committee (itself a part of the Department of Specialized Medical Assistance of the Ministry) primarily an advisory and "expert" organization, has the primary duties of recommending new pharmaceutical preparations and of removing pharmaceuticals from the market when they become obsolete. Within that committee there is a commission "on instructions and informational materials" which presumably prepares literature giving knowledge about the existence and the application of new pharmaceuticals. The second organization concerned with pharmaceuticals is also lodged in the Health Ministry and is entitled the Department of Pharmaceuticals and Medical Technology with a quality inspectorate. The main functions of the department are to insure the standardization of drugs produced in the Soviet Union, to edit the Governmental Pharmacopoeia U.S.S.R. and make periodic additions to it, and to examine complaints of nonstandard production.[7]

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[6] Field, Mark G., "Pharmaceutical, Pharmacies, and Pharmacists in Soviet Russia," American Professional Pharmacist, vol 25, January, February, March 1959 (January, p 27); also, Field Mark G., "Die Pharmazie in der Sowjetunion," Schweizerische Apotheker Zeitung, 95 (April 1957) pp 303–311

These articles are worth consulting for the general background of the Soviet pharmaceutical industry. Another useful review is: Schulz, H. G., "Contemporary Conditions in the Soviet Medical Industry," Review of Eastern Medical Sciences (Munich) April–June 1956, pp. 7–17

[7] For a more thorough description see "Uchebnik Organizatsii Farmatsevticheskogo Dela" (Textbook on the Organization of Pharmaceuticals) (Moscow: Medgiz, 1961).

Neither of these organizations seems to incorporate a specialized, active, and dynamic system for disseminating information about new drug products to the physicians practicing in the U.S.S.R. that in any way parallels the work done by the American drug industry's detail men. Rather the picture appears to be one of general announcements in the medical and sometimes the lay press and other media of mass communications,[8] when a new compound or agent is cleared for production. Special information supplied to physicians often amounts to nothing more than simple one-page "flyers." These steps, it is clear, makes the information minimally available, and presumably the physician with initiative and interest could keep informed thereby.

Unfortunately, this assumption about the physician's initiative and his ability to keep up with new medical products seems to be as unfounded in Soviet society as it is in the United States. The belief that if information or products are made available, he will automatically make use of them is not borne out by the evidence. The expectation that he will dutifully note such drug innovations and promptly prescribe them to the next patient to which they apply seems to be expecting too much under contemporary conditions.[9] Rather, it would seem that more active methods are necessary to force feed this information to physicians. And to some degree, the Soviet medical literature reveals that Soviet medical authorities are well aware of the communication problem and are attempting to take certain steps that will remedy it. Complaints about the inadequacy of information about new products are endemic. Eight such complaints were registered in one source "Meditsinskii Rabotnik (Medical Worker)" [10] during the first 7 months of 1961. The flavor of these complaints can be gathered from the following fairly typical extracts:

"* * * information about new drugs is given irregularly so that practicing physicians do not know about them and are deprived of the possibility of using them. The process of replacing old-fashioned drugs by new and more efficient ones, is too slow." [11]

"It is necessary to point out that as yet physicians and pharmacists are poorly informed about new drugs. Any information is purely accidental. The pharmacological council has advised the State Publishing House of Medical Literature to publish as soon as possible four publications on new pharmaceutical products." [12]

"Too much time is wasted in pharmacies on the compounding of prescriptions, and this is only because the physicians do not know about the precompounded drugs. Obviously, only very few general practitioners follow the literature in which the new drugs are described On the other hand, pharmacy employees do not inform physicians about existing drugs. *They do not come to the polyclinic and do not promote the new pharmaceuticals.*" [13]

"The head of the Department of the Pharmaceutical Network of the Main Pharmaceutical Administration of the Ministry of Health of White Russia worries. We could invite physicians to meetings of pharmaceutical workers, but they do not come to us, do not listen to us." [14]

This picture is indeed an ironic inversion of the situation in the United States. Missing are the complaints about junk mail and pill peddlers. While there may be difficulties associated with an overpromoted drug system, the Soviet experience indicates that underpromotion produces its own characteristic problems. Clearly, the quotations cited above indicate a high degree of dissatisfaction with the speed with which information about new drugs is disseminated and put to use.

Efforts have been made, in recent years in the U.S.S.R., to give greater publicity to new pharmaceuticals. For example, polyclinics have been requested to set up

[8] See, for example the Medical Worker of July 12, 1960, p. 4 for an example of such announcement. Under the title "New Preparation," Dinezin is described as a new drug with antihistaminic effect. It briefly indicates the types of action it has, and the kinds of conditions for which it is indicated The dosages and form in which the drug is available are given as well as suggestions for its use In Medical Worker of Jan 12, 1962, p. 3, it was announced that the Pharmacological Committee of the Health Ministry U.S.S.R. had assigned new names to some already compounded pharmaceutical preparations of a complicated nature The chemical compositions were given.

[9] The difficulty of the physician's task of keeping informed while attending to his other tasks is spelled out in Bauer, Raymond A., "Risk Handling in Drug Adoption," Public Opinion Quarterly, vol 25, winter 1961, pp. 546–559.

[10] Published semiweekly.

[11] Medical Worker, Apr. 4, 1961.

[12] Ibid. June 6, 1961.

[13] Ibid. May 19, 1961, italic added.

[14] Ibid. July 20, 1961.

special exhibits or displays of new pharmaceuticals. According to the Soviet press, however, these displays are often nonexistent. Nor are there listings of currently available drugs, presumably due to the intervals between the appearances of new editions of the official pharmacopoeia.[15]

Not only is the system of dissemination of information taken to task by Soviet critics, but so are the recipients of such information, the physicians themselves, who are criticized for not displaying enough initiative. Recently the Health Minister of the U.S.S.R. said:

"It is absolutely necessary that every physician should know what precompounded drugs there are on the market. It is our important task * * * to criticize those physicians who think that the knowledge they acquired at the university will suffice for their whole life." [16]

As we have seen, some of the remedies proposed by the Soviets (and to some degree implemented by them) appear to be quite orthodox by our standards: publication of pamphlets, exhibits, listings by the Health Ministry and so forth. Even more interesting and significant, however, is the fact that representatives from the pharmacies or from pharmaceutical warehouses or subdepots are now being sent out to the clinics to inform physicians on what new pharmaceuticals are available and, in turn, to find out their needs and requirements. A rose by any other name, these representatives are, doubtless, the functional equivalents of the U.S. drug industry's detailmen. And, significantly, Soviet criticism is leveled at those pharmacies that do not use detailmen, or do not engage intensively in promotional activity, and praise heaped on those that do. For instance, an article in the Medical Worker (Sept. 20, 1960, p. 3) approvingly described how a representative from a pharmacy periodically visited physicians and appeared before assemblies of doctors and provided information about drugs.[17]

Such assemblies make it possible, of course, for the representative to reach a wide range of physicians, since these assemblies take place periodically at the district polyclinics where physicians in the community, all working under one roof, see their patients. One might well wonder, however, whether such mass presentations adequately can replace the person-to-physician presentation provided by the U.S. detailman.

There is a definite but subtle overtone of unsocialism to complaints that representatives of pharmacies are not sufficiently diligent in promoting new drugs. But, even more unorthodox is the proposal of vigorous advertising. Historically, advertising has been regarded by Soviet authorities as a socially wasteful device for foisting off on people goods they did not need. Since this attitude has, of late, undergone some modification, the advertising of pharmaceuticals has come to be advocated as a means for keeping doctors informed. For example, an article toward the end of 1960 complains that new pharmaceuticals do not become immediately available to practicing physicians. Why? Because of "a lack of well established information about medical novelties." The article advocates an information service via press, radio, TV, leaflets, and so forth.[18]

A more recent article entitled "The New Form of Advertisement," had this to say:

"* * * together with such methods of advertising as advertising in the local newspapers, through radio, exhibitions and lectures about new pharmaceuticals * * * advertising in pharmacies will undoubtedly have to be perfected and improved. The most convenient and efficient forms of advertisement must be exploited. There is no doubt about it that these forms of advertisement, radio and tape-recorded announcements, will find most widespread application in our country." [19]

Import for the United States

Soviet experience with a functionally inadequate informational service for pharmaceuticals, and the recent Soviet awareness of the role that can be played by various forms of advertisement (whether detail men or increased advertising activities in the mass media) should not be taken as justification, per se, of any level of expenditure on any one promotional practice. It should alert us, however, to a closer examination of the byproduct of promotional activities in-

[15] Medical Worker, June 6, 1961.
[16] Aptechnoe Delo (Pharmaceutical Affairs) No. 2, 1961, p. 65.
[17] On presentations to assemblies of physicians also see the Medical Worker, May 24, 1960, p. 3.
[18] Medical Worker, Nov. 11, 1960, p. 4.
[19] Pharmaceutical Affairs, No. 2, 1961, p. 65.

the selling of pharmaceuticals. A distinction between manifest and latent functions may be useful in this context." The manifest function of promotion, advertising, and detail men, at least in our society, is to sell doctors by persuading them to prescribe a certain product by its brand name. But this, as we have seen, is often looked upon with suspicion as a kind of maneuver that eventually increases the prices of pharmaceuticals. Furthermore, such activity has been criticized as being of no social value and should, therefore, be eliminated. Overlooked is the latent and probably largely unintended consequence of such promotional activities, that is, they serve as transmission belts for new information from the manufacturer to the consumer (i.e., to the physician and his patient). That such a latent function is not superfluous is indicated by the inadequacies (in this respect) of the Soviet system in informing the medical profession about pharmaceutical innovations, and by the efforts made by the Soviet health authorities to create an institutional system that would remedy these inadequacies. In the light of this examination, then, the question arises about the wisdom of a frontal and wholesale assault on current American practices in the Pharmaceutical field. One might ask whether the promotional practices of the ethical drug firms are as antisocial in their consequences as some would have us believe. One might even raise the question as to what might be the social "costs" involved in eliminating these practices. There is no doubt that, in some instances, abuses have taken place. The question is whether the baby should be thrown out with the bath water. Considering the richness of our economy and the value attached to human life and welfare in the United States, we presumably would be even less disposed to tolerate slippage between availability of drugs and their use in practice than the Soviets.

SOVIET NONCOMMERCIAL DRUG RESEARCH

In both the Soviet Union and the United States, the second large area of complaint centers around pharmaceutical research. We have already seen the charges leveled against the American industry. But, what is the Soviet complaint? It is essentially that unnecessary delays are experienced in getting valuable results of pharmaceutical research into effective use by doctors and patients owing, first, to problems in communication between institutes of research and production establishments, and second, to bureaucratics delays, sometimes severe, between governmental testing and evaluation of new drugs and ultimate approval for production.

We hasten to add that the only sure thing about research is that it is inefficient. The very best of organizational setups would almost certainly be marked by easily noticeable inefficiencies. Hence, we would not use these Soviet charges as "proof" of the superiorities of the American research establishment; nor would we argue for or against the virtues of university or governmental research in comparison with commercial research. We submit, however, that the Soviet experience shows that critics of the American industry have glossed over the problems involved in the transition of a drug discovery from research into production.

To anyone familiar with a reasonably technical industry, the steps between laboratory research and production are far from trivial.[22] Under the best of circumstances this involves the close day-to-day collaboration of laboratory, engineering, and production personnel, involving adjustments, redesigning, and rethinking that may go on for months, and perhaps in extreme cases for years before the laboratory product has been debugged in production.

Since Tsarist times, scientific research in Russia and the Soviet Union has been carried out primarily in research "institutes" separate from universities and industry. The closest approximation in the United States might be a Government organization such as the National Institutes of Health. Research in pharmacology takes place in institutes mainly under the aegis of the Academy of Medical Sciences and of the Ministry of Health of the U.S.S.R. Production, on the other hand, takes place in organizations that now are under the control of regional economic councils called sovnarkhozy. An approximate parallel in the United States would result of research were performed in university and Government laboratories, and production accomplished by private firms.

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[21] The clearest exposition of what is meant by these terms can be found in Robert K. Merton's "Manifest and Latent Functions," in Social Theory and Social Structure (Glencoe: The Free Press, 1949) pp 21–81.

[22] A description of the organizational problems of handling this transition in the American pharmaceutical industry can be found in Lawrence Paul, et al, "Organizational Behavior and Administration," Haig Chemical Co., pp. 496, ff., Irwin, 1961.

As a result of the Soviet arrangement, there are difficulties of communication and coordination between institute and factory which constitute, if we may take the word of Soviet sources, a major bottleneck in getting pharmaceuticals into production. To quote a recurrent theme in the Soviet medical press: "* * * it is essential * * * that research and production be brought closer together so that research accomplishments may be put into practice more rapidly." [22] A measure of the seriousness of this problem is the fact that in the first 9 months of 1961 this topic was brought up five times in the Soviet monthly journal, Medical Industry.

The picture that emerges is that of an institutional arrangement definitely inadequate to the complexities of converting a laboratory product into something that can be produced economically in volume. Note the tone of the following complaint:

"* * * the chemico-pharmacological establishments are slow in bringing a number of the new pharmaceuticals into production. Many pharmaceuticals which have been approved for use in general practice are not yet on the market. The planning bodies do not perceive clearly enough the conditions which exist in the factories when pharmaceuticals are produced. Representatives of the factories noted that the technical instructions received from the institutes frequently do not meet present day requirements. Quite often when they are followed they cause great difficulties and high financial losses." [23]

Not only are the instructions received from the research institutes often impractical, but apparently it often takes a good deal of time to develop an adequate set of directives.

"It is obligatory that the quality of instructions and other technical documents from the institutes to the pharmaceutical factories be improved. There are cases when factories have to waste considerable time, sometimes even a year, in getting the instructions from the institute spelled out." [24]

Perhaps we may grant the wrap-up of this particular complaint to one Dr. Timakov who spoke as follows:

"* * * We have too few scientific research institutes concerned with the search for new pharmaceuticals. It is a secret from no one that in our country the period from the birth of a new preparation in the laboratory to its introduction into practice is on the average from 3 to 4 years. In some cases it is 7 years." [25]

Dr. Timakov then called attention to a Soviet discovery which was being produced abroad while the technique of production had not yet been mastered at home. He mentioned 14 preparations which had been approved, but only two of which were being produced, and then launched the standard complaint about the extraordinary delays resulting from the institutional separation of research and production.

It may be, of course, that Soviet critics of their own system are over-reacting to its difficulties. But, to some Soviet authorities, at least, the liabilities of the present institutional arrangement are obvious. If it were matched against the American system it is conceivable, but certainly not proven, that the Soviet arrangement could produce, on a ruble-for-ruble, or man-for-man basis, as many or more laboratory products as could the U.S. industry. But, the testimony of the well-informed Soviet sources is that the separation of research from production tends to produce substantial delays in the availability of drugs to physician and patient.

The speed with which the American ethical drug industry can move a drug from research into production offers a sharp contrast to Soviet slowness. Under ordinary circumstances, an American pharmaceutical manufacturer will begin to work on production problems as soon as laboratory and clinical tests suggest the clinical and commercial worth of the drug. The development of production methods, and, in fact, the stockpiling of stores of the drug are usually done in anticipation of approval by the Food and Drug Administration. Thus, in most cases, lag between Government approval and the availability of the drug is nonexistent. Again, one may wonder at the social costs that might result, in the American situation, from an institutional separation of research and production.

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[22] Meditsinskaia Promyshlennost' (Medical Industry), No. 9, September 1961, p. 13.
[23] Medical Industry No. 5, May 1961, p. 63.
[24] Medical Industry No. 9, September 1961, p. 14.
[25] Meditsinskii Rabotnik (Medical Worker) July 5, 1960, p. 3.

CONTROL OF QUALITY AND SUPPLY OF DRUGS

The separation of drug research from production in the Soviet Union is not the only cause of delay. An additional cause is the elaborate bureaucratic procedure for the screening of new drugs.[25a] Here, once more, we find repeated complaints in the medical press. The reasons for delay seem to be several: the complexity of the procedure, the conservatism of the criteria employed, and some overloading of personnel and facilities. We find, for example, a Dr. N. Levin complaining in Medical Worker that: "Already 4 years have elapsed since biliarin was proposed. This interval is sufficient to study the drug from all sides, to test it clinically and, having established its useful action, to legalize it and place it into the practice of medicine. But this has not yet been done. The Pharmacological Committee until now has not delivered the drug its 'right to life' and this is why it is not being produced anywhere." [26] Or, that "The Mechnikov Institute has been waiting 2 years for the verification of the immunity of the vaccine * * * " The Soviet reporter attributed the disagreement between representatives of the Controlling Institute and the academic body of the Mechnikov Institute to the lack of a common method of control testing, combined with an adamantly negativistic point of view on the part of the representatives. "They speedily developed a doctrine which amounted to 'to forbid'." [27]

Examples, such as these are probably extreme. We have seen no estimates of the average time required for the screening of a drug. However, the lesson involved is sufficiently straightforward that there is no point in further documentation or elaboration. Neither in this country nor in the Soviet Union has any responsible person denied the need for some form of official screening of drugs. But in both countries there are complaints that introduction of drugs is unduly delayed. Obviously, there are a series of factors to be balanced off against each other: the cost of a more adequately staffed and equipped screening system, the dangers of passing unsafe drugs, the dangers of delaying the introduction of new drugs, and so on. Any such screening system will always consume some time; therefore, proposals to extend the responsibilities of Government screening authorities must be made with realistic consideration of the delays involved and the need for increased facilities and personnel.

Of more interest, in the light of what is known about problems of quality throughout the Soviet economy, is the question of the quality of drugs produced by Soviet production establishments. Unfortunately our direct knowledge is quite incomplete. However, what we do know fits so well with the rest of the Soviet scene that we can perhaps venture to fill in some gaps from our generalized knowledge.

Complaints in the press about the poor quality of Soviet pharmaceuticals are frequent. "The struggle for better quality drugs was renewed with greater strength after the 22d Party Congress," writes one critic.[28] Another asserts. "Our industry does not always produce medicaments of good quality. And so it happened, for instance, that from the overall number of pharmaceuticals which were sent this year for evaluation to the Central Pharmacological Research Institute, more than half were rejected, mainly ampules. The rejects were found especially often in the products of the Khabarovsk and Novosibirsk factories, in the Kharkov factory called 'Zdorovie Trudiashchikhsia,' and in the Moscow factory named 'Semashko.' The above examples show that the workers of the chemicopharmacological industry do not always work conscientiously." [29]

The head of the Biological-Chemical Laboratory for the Standardization of Drugs of the Central Pharmacological Research Institute complained: "Every year, there is an increase in the production of various drugs in our country. Many of them are sent for evaluational testing to the Central Pharmacological Research Institute. In the last year, for example, 112 various drugs were sent to us—ampules, tablets and others. And, it is deplorable that 75 percent of them did not meet the requirements of the official Governmental pharmacopoeia and the technical standards. In the first 3 months of the current year, the Institute received some dozens more of pharmaceuticals and this time again, from the 74 tested, 58 did not meet the requirements." [30]

[25a] Cf. Schulz, op cit. pp. 10–11 for a description of this system.
[26] Aug. 16, 1960, p. 3.
[27] Ibid.
[28] Medical Worker, Dec. 22, 1961.
[29] Medical Worker, Feb. 24, 1961.
[30] Medical Worker, July 14, 1961.

The fact that there is an endemic problem of quality facing the Soviet drug producers cannot be doubted by anyone familiar with the medical press of that country. The reasons for this problem seem also to be clear. As is generally true in Soviet industry, quality control is not well built into the manufacturing process.[31] The Soviets rely on testing done by an independent inspection system, in this case the "Controlling Analytical Laboratories of the Pharmacological Administration."[32]

Efforts to maintain quality control by policing via an external inspection system has been one of the conspicuous failures of the generally successful Soviet economy. In various ways this failure is being acknowledged throughout the economy. The first signs of corrective steps that might be taken in the pharmaceutical industry have occurred recently. One writer in the Medical Worker stated:

"At the present time, the testing of the quality of medicaments is carried out, as a rule, in the Controlling Analytical Laboratories of the Pharmacological Administration. This work ought to be done first of all in the factories themselves by their technical control branches. It is really there that the necessary conditions should be created for the continuous control of the quality of the entire output. * * * The time has come when we are justified in demanding that the medical industry deliver production only of the first quality. For this purpose it is indispensable to organize closer contact between the industry and the network of pharmaceutical specialists. The managers of factories should give detailed accounts at the meetings of pharmaceutical societies. In the immediate future there will take place an all-union scientific convention in which representatives of the chemico pharmaceutical industry, of research institutes, and pharmaceutical workers will take part. The convention is devoted to the problem of the improvement of the production and control of quality of the medicaments in ampules."[33]

This attempt to get the producing organization to take responsibility for quality has become relatively familiar in recent years in the Soviet Union. To gain perspective, we must both back up a few years and look at the Soviet economy in its overall aspects.

Until the Russian revolution, the experience of both Marxist and non-Marxist economists had been exclusively with capitalistic economies. There was among all economists (among Western non-Marxist economists whose experience is conditioned by modern capitalism there still is) a tendency to take quality for granted. Four decades of running a socialist economy have cured Soviet economists and administrators of this disposition. The central feature of this experience has been the extraordinary difficulty in maintaining quality of products in a socialized economy.

Until relatively recently the task of inspection was left in its virtual entirety to the Government bureaucracy. There were three difficulties with this system: (1) Quality remained substandard. (2) Minimum standards also became maximum standards. Manufacturers had no economic incentives (and Soviet manufacturers do operate according to economic incentives) to produce any quality beyond the minimum required by the established standards. (3) In addition to the fact that quality continued to be unsatisfactory, the system of inspection proved to be both cumbersome, expensive, and, to a large extent, ineffective.

Recently, The Soviet decision has been to pass on this inspection function, at least in part, to the manufacturer and the consumer. Each factory has been required to affix to its products some identifying mark. It will be remembered, for example, that in the complaints about poor quality mentioned above, the factories of origin were mentioned by name.[34] At present, manufacturers in many areas are being urged to adopt a trademark which really is a somewhat more overt version of the production mark, this making it still easier for the consumer to identify the factory; the hope here is to instill in the producers a sense of identification and pride in their product and a feeling of responsibility for their quality. It is hoped further that each enterprise will push its quality above minimum standards in order to compete effectively with other enterprises.

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[31] This argument depends heavily on the work done by Goldman, Marshall I., "Product Differentiation and Advertising: Some Lessons From Soviet Experience," The Journal of Political Economy, August 1960, pp. 346–357.

[32] Cf. Medical Worker, Nov. 28, 1961.

[33] Ibid., Nov. 28, 1961.

[34] Often the responsibility also tends to be personalized by the publication of the factory manager's name.

In support of trademarking, two Soviet economists have delivered remarkably capitalistic sounding proclamations:

"* * * the trademark makes possible for the consumer to select the goods which he likes, the one which is produced by one firm out of a number of homogeneous * * * goods made by other firms."

"This forces other firms to undertake measures to improve the quality of their own product in harmony with the demands of the consumer. The trademark promotes the drive for raising the quality of production." [32]

At the present time, we have no evidence that the Soviet Union is pushing trademarks or brand names in its pharmaceutical industry. To the best of our knowledge, all Soviet factories producing the same type of drug use the same name for it, and often the same type of packaging. While no factories have made a deliberate attempt to publicize their names, it is nonetheless true that the consumer can identify from a careful reading of the package which factory or which economic regional council is responsible for its manufacture. It should, perhaps, be indicated at this point that there are some differences between the pharmaceutical firm in a socialized economy and in a capitalistic economy. In the first instance, the factory comes into being as a result of a specific decision on the part of the appropriate authorities. Its function is to produce certain goods. Its manager or managers stand to benefit (through bonuses) from an overfulfillment of production plans. But there is much less stress on control of qualitative indexes, and the life of the factory (in the economic sense of a profitable institution) is not so much at stake as it would be in a capitalistic competitive economy.

At the same time, recent developments on the Soviet economic scene would lead one to believe that the situation in the pharmaceutical industry may not be essentially different from that in the consumer goods industry where trademarks have been, or are in the process of being, developed. If responsibility for quality control is to be placed prominently on the factory, the logic of the situation would be that the factory would then try to give itself a distinctive identity in order to capitalize on the superior quality of its products. We are arguing here that if we take on face value the logic for trademarks that Soviet authorities have employed in other areas of the economy, it would appear to apply equally in the pharmaceutical industry. Soviet experience with quality, both in the pharmaceutical industry and in other parts of the economy, would not encourage us to dismiss casually the use of brand names for drugs.

Interestingly, a similar problem arises with respect to the selective shortages of some drugs, though to the best of our knowledge no student of the Soviet economy has yet interpreted this specific phenomenon in the terms we are about to use. The general problem is well known.

Since the midthirties, Soviet pharmaceutical manufacturers, like other Soviet enterprises, have been on a "profit" (xhozrashchet) basis. They are assigned quotas of goods to produce, prices are put on the various products, and the enterprise earns a "profit" for meeting and surpassing its quota. Pricing systems being what they are, some products usually turn out to be more profitable than others. From this factor grows the perennial Soviet problem of the "product mix." Sanctions are employed (or attempted) to get the required mix of products out of the enterprise. But, in one way or another, factory administrators manage to evade controls on the product mix so as to maximize their profits.[33]

Soviet press reports regularly complain of shortages of drugs and medical supplies. Among these shortages are frequently the most prosaic of items such as glucose, talcum powder, tincture of iodine, bicarbonate of soda, and even saccharin.[34] In fact, Soviet pharmacies seem to prefer to stock costly medicines which will produce a high profit for a small turnover, as is obviously the case for the antibiotics whose high retail prices so scandalized the Health Minister.[35]

On the basis of what is standard practice across the board in Soviet industry, it must be assumed that selective shortages in production occur as a result of the most profitable items.

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[32] Genkin and Fialkov, quoted by Goldman, op. cit., p. 351.

[33] For a description of the intricate games that a factory manager can play in this system see Berliner, Joseph, "Factory and Manager in the U.S.S.R.," Harvard University Press, 1957.

[34] Medical Worker, July 22, 1960, p. 4.

[35] Field, "Pharmaceuticals, Pharmacies, etc.," February, p. 107.

will be associated with that quality and that this will do him some good with his customers. Similarly, the probability of a manufacturer carrying a reasonably full line covering relatively low-profit or loss items is greater if he feels that this gives him a customer franchise. This, manifestly, can happen only if the doctor recognizes the full line as an entity, or, to speak plainer English, if the line of drugs is promoted under a single name.

CONCLUSION

A paper such as this is an open invitation to the reader to perceive us as having said many things which we had no intention of saying. For example, we have not defended or even commented on the profit level of the American ethical pharmaceutical industry. Nor, have we advocated any particular level of expenditure for drug promotion and/or research. We repeat the thought with which we began this article: among the various ways of doing things that reasonable men are likely to try, there are likely to be both advantages and disadvantages. Being acquainted both with the Soviet medical system and to a lesser extent with the Soviet drug industry, and with the American pharmaceutical system we thought it might be instructive to match these two systems against each other to see what could be learned.

Specifically, we were interested in seeing whether Soviet experience threw any light on the alternatives that have, at times, been proposed to the policies of the American pharmaceutical industry. We found that these alternatives as practiced in the Soviete Union seem to have their own built-in liabilities. It is our guess that these liabilities are not necessarily linked to the other features of Soviet society. There are, of course, difficulties of the drug industry that are distinctive of the Soviet scene. For example, drug distribution is at times grossly inadequate because of inefficiencies in the overall distribution and retailing system. Some aspects of shortages are due to the Soviet system of planning and allocating supplies, etc. We have not dealt with these distinctively and exclusively Soviet phenomena, but solely with those which might realistically or semi-realistically be tried in our economy, and which in our judgment might tend to produce similar problems if transplanted.

Perhaps the journey overseas was not necessary. It could be argued that a reasonable man might well have anticipated our conclusions, namely:

1. Separation of research from production, whatever its other merits may be, slows up the process of getting laboratory items into production.

2. An underpromoted pharmaceutical system leads to substantial lag in the introduction of new drugs.

3. Quality control belongs preferably with the manufacturer and is more likely to take place if he has a significant realistic motive for undertaking it. Customer preference is such a reason.

4. Customer preference is also a stimulus for maintaining a full line of items, some of which may be unprofitable.

It may be that social policy will demand substantial reforms in the American pharmaceutical industry. Before we undertake them, it might be wise to remember Herbert Spencer's gentle admonition about remedial measures:

"You see that this wrought-iron plate is not quite flat; it sticks up a little here toward the left * * * how shall we flatten it? Obviously, you reply, by hitting down on the part that is prominent. Well, here is a hammer, and I give the plate a blow as you advise. Harder, you say, still no effect * * * the prominence remains * * * as great as ever—greater, indeed * * * look at the warp which the plate has got near the opposite edge. Where it was flat before it is now curved * * * instead of curing the original defect, we have produced a second. Had we asked an artisan practised in 'planishing' * * * he would have told us that no good was to be done, but only mischief, by hitting down on the projecting part * * * the required process is less simple than you thought. Even a sheet of me...l is not to be successfully dealt with after those commonsense methods in which you have so much confidence." [41]

This quote, is not a plea for inaction. It is only a plea for wise caution and careful analysis.

[41] Herbert Spencer, The Study of Sociology, New York, 1875, pp. 270–271.

RAYMOND A. BAUER

Dr. Bauer is professor of business administration at the Harvard Graduate School of Business Administration and a consultant to Arthur D. Little, Inc. He has been a consultant to business, government, and semi-public organizations on problems of social communications, market research, organizational functioning and administration, and international relations. He has taught and done research on consumer behavior, social and mass communications, social psychology, research methodology, and administrative practices. He also has considerable experience in the administration of social research.

Dr. Bauer is the author or coauthor of many studies on topics mentioned above, including two books (one forthcoming) on American business and foreign trade policy, and four books on Soviet affairs which are in a considerable measure concerned with the functioning of large-scale organizations.

In 9 years' work in industry, he served as shipping clerk, foundry laborer, materials tester, stock clerk, and chemical analyst of ferrous metals.

Dr. Bauer served in the Naval Reserve during World War II as a Russian language officer.

He received his Ph.D. in social psychology from Harvard University and has taught at Massachusetts Institute of Technology and the College of Liberal Arts at Harvard, as well as doing research at the Russian Research Center, Harvard, and the Center for International Studies, MIT. In addition to being a member of various professional organizations, he holds elective offices and various committee posts in the American Psychological Association, the American Association for Public Opinion Research, and other such societies.

Among his professional honors are: Fellow of the American Academy of Arts and Sciences, and fellow of the Centre for Advanced Studies in the Behavioral Sciences.

MARK G. FIELD

Dr. Field is associate professor of sociology at the University of Illinois and a consultant to Arthur D. Little, Inc. He is currently teaching at the Harvard summer school. Dr. Field has participated in research work concerning general and medical sociology, Soviet social institutions, and Soviet medical organizations. He has had considerable experience in directing and carrying out research projects in these areas.

Dr. Field received his A.B., A.M., and Ph. D. degrees from Harvard University. In his graduate work he concentrated on Soviet affairs by studying in the regional studies program (Soviet Union) and participated in the Harvard project on the Soviet social system sponsored by the U.S. Air Force and carried out by the Russian Research Center.

He has visited the Soviet Union twice and also Czechoslavakia and Poland pursuing his research work in the field of Russian medicine. In addition he has participated in two extensive research projects: one on hospital utilization as affected by the use of so-called wonder drugs sponsored by the Health Information Foundation; and the other on mental illness sponsored by the U.S. Congress.

Dr. Field served in the U.S. Army in 1944 through 1946 primarily as an interpreter in liaison work between American and Soviet forces.

He is the author of "Doctor and Patient in Soviet Russia" (1957), and joint author of "New Perspectives in Mental Patient Care" (forthcoming). He is currently at work on "An Introduction to Soviet Socialized Medicine." He has also published, in addition, numerous articles on the Soviet social and medical scene. He has lectured to numerous groups including the National War College, the Army War College, and the Judge Advocate General's School.

Among his professional honors are fellow of the American Sociological Association, and member of the American Association for the Advancement of Slavic Studies.

The CHAIRMAN. Mr. Dingell, do you have any questions?

Mr. DINGELL. No questions, Mr. Chairman, thank you.

The CHAIRMAN. Mr. Schenck.

Mr. SCHENCK. Thank you, Mr. Chairman.

I am not quite certain just what Dr. Bauer is trying to say. I do not know yet whether he thinks that the American system is better than the Soviet system or vice versa.

Mr. BAUER. I was quite aware of the fact that the most probable question that would be thrown to me was that. I have tried very assiduously to avoid any question as global as that.

Mr. DINGELL. Doctor, you do not need to be fearful of being a capitalist in this committee.

Mr. BAUER. I still have to maintain my posture as a scholar.

What I have tried to do is to point out that certain institutional arrangements have produced the type of consequences you have in the Soviet situation. I am sure we have our problems too, and I do not want to have to explain those two guys who were flying around upstairs last week on the basis of the fact that our pharmaceutical system seems to work a little better. So I have not taken a stand on the overall economy, but I have tried to spell out what the implications of certain institutional arrangements were.

Mr. SCHENCK. It seems to me, Dr. Bauer, that the tenor of your statement here is that the socialistic system of manufacturing drugs by allocating certain preparations to certain factories at a given rate of profit is better, and yet you also stated—what about the cost of these to the people?

Mr. BAUER. I actually think that their system is functioning worse for them now than ours is functioning for us. By allocating these quotas and setting prices, they are not getting the drugs out that they want in either the quantities they need, nor are they getting the quality because the factory manager fudges in order to maximize his profits.

The familiar example of this in the Soviet situation, I shift to tractors because the example is easier to communicate, is, a fellow will get such and such a price for delivering tractors and such and such a price for delivering spare parts. It usually turns out that it was more advantageous to him to deliver tractors, so he did not deliver spare parts and you had tractors breaking down all over.

As far as we can tell, apparently the same thing is happening in the pharmaceutical industry. This is analogous to the generic manufacturer who produces each drug on its own profitability, and when he does that, why he produces the most profitable drugs and lets the least profitable ones go.

Now the gentlemen we have had here today all come from companies which are producing a range of drugs and they are producing many drugs which are not as profitable for them because they want to maintain their reputation with the doctor.

Mr. SCHENCK. The American system is also highly competitive. Apparently here you take out competition. Apparently here you remove the incentive.

Mr. BAUER. There has been a quotation in the New York Times within the last few months in which a Soviet Communist has lamented the fact that we have competition and this serves as a yardstick for judging our products and keeps our producers on their toes. I could not be clear from the New York Times article whether this fellow was actually advocating return to a competitive system or whether he was just weeping, but he obviously was aware of the fact that there were some advantages to a competitive system.

Mr. SCHENCK. Do I understand that under the Soviet system here that they use the generic name?

Mr. BAUER. For practical purposes, they use the generic name. That is, each factory does not have a separate name. Chloramycetin I think is promoted as Chloramycetin, which is a brand name here but it is the only name available there, so it is for practical purposes the generic name. It is not a chemical name, but it is the same name regardless of which factory produces it.

Mr. SCHENCK. From the few generic names that I have looked at, if we require generic names to be put on to the label of a prescription drug here, we are going to have to increase the size of the container.

Mr. BAUER. This is a problem.

Incidentally, they are actually traveling the road in the opposite direction from us. They have the factory put its name on the box so that the factory can be located, but as I have indicated, there is good reason to suspect that they may be going for brand names in drugs fairly shortly because they have been doing this in other parts of consumer goods, so that competition, in effect, will take place.

Mr. SCHENCK. When the physician, if he is free to prescribe, does prescribe a certain drug over there and the patient goes wherever he goes, the drugstore——

Mr. BAUER. The drugstore, yes.

Mr. SCHENCK. To get that prescription filled, is the pharmacist required to put the name of the company from which the drug came and also the generic name and so on onto his label if the druggist buys it in a quantity?

Mr. BAUER. I could turn to Dr. Field for that.

Mark, do you want to check me on that? You have had this happen to you.

Mr. FIELD. The drug's name——

Mr. SCHENCK. Might you identify yourself for the record?

Mr. FIELD. Mark G. Field, assistant to Dr. Bauer in the work we did on the Soviet comparative material.

If the prescription is for a prepackaged item, then, of course, the generic name will be printed on the item. If the prescription is for an item which is compounded by a pharmacist, then the generic name or whatever the name of the drug is would be written on the prescription and on the label of the drug itself.

Mr. SCHENCK. Then in that case the druggist does not remove the label of the manufacturer and put it on the prescription label?

Mr. FIELD. No, sir.

Mr. SCHENCK. Is that correct?

Mr. FIELD. Yes, sir.

Mr. SCHENCK. All right, Mr. Chairman.

From what you have said here, it seems to me that you have only proven that the U.S. pharmaceutical manufacturers and the medical profession and health care system in the United States is far superior to the Soviet Union.

Mr. BAUER. I am delighted you came to that conclusion.

Mr. FIELD. I was thinking that this was an example, what Mr. Schenck said, an example of what was pointed out to the committee earlier this afternoon with reference to giving authority to the Food and Drug Administration to determine the efficacy of a drug, because there are so many different opinions about it.

Now I got the impression from your statement that you tried to be perfectly objective about it and not show any prejudice for the purpose of this statement to the American system or the Soviet system, but when you wound up with that short punch paragraph saying: "Be very careful before you change our system, you might get into the other system," I gathered from what you said finally that you used this analysis to impress upon us that we should not make the changes because we might tend to go in some other direction.

Mr. BAUER. This is the professorial soft sell; I hope it worked.

Mr. SCHENCK. Mr. Chairman, I call attention to the fact that Dr. Bauer is a psychologist.

The CHAIRMAN. I also notice from reading his biographical statement that he is professor of business administration at Harvard University.

Mr. SCHENCK. That ought to really fix it up.

Mr. BAUER. It is really three people.

The CHAIRMAN. Doctor, you said factories are allocated quotas of drugs used for which they receive an assigned "reasonable" profit.

Mr. BAUER. Yes. Well, the reasonable profit, you know——

The CHAIRMAN. Is this done in Russia?

Mr. BAUER. Actually, what the factory gets assigned is a certain quota to produce and they get two quotas. One is a physical output quota and the other is a financial quota, and prices are assigned to each of the items.

Now once they have met their quotas, the factory manager particularly gets premiums for exceeding that quota.

The CHAIRMAN. In other words, what you meant, he got a bonus for doing an exceptionally good job?

Mr. BAUER. It was a little bit too long to develop the point fully. I figured that the reasonable profit in quotes would communicate the essence of this.

The CHAIRMAN. Thank you very much.

Mr. SCHENCK. Dr. Bauer, you would indicate that the Soviet system is a planned economy?

Mr. BAUER. They try.

The CHAIRMAN. I am like a lot of other people you know. I spent 3 weeks in Russia one time and I found out all about their operation. But from what I have heard and observed they do a pretty good job of their planned economy too.

Thank you very much for your statement.

Professor Field.

Mr. FIELD. The only comment I would like to make on the planning system is that on the surface it looks very rational, very logical, very economical.

In practice it is often just the opposite. I am reminded of a metaphor that was used by, I believe, Dr. Carl Polani on the beauties of rational planning. Let's say you have a pile of potatoes that you are trying to place into a sack with the least amount of waste space. There are two ways you can do it.

One way you can make profiles, cuttings, and calculations on each potato available, code them on IBM machines and find out the best and most rational and most economical way of doing it. It would

take about 6 months and perhaps half a million dollars, but it could be done.

The other way is simply to dump the potatoes and shake the sack. I mean the result will be within a few percentage points of the first one.

And I have seen quite often that the free enterprise system with the mutual adjustment, mutual regulations of competition, does the job much better than the so-called rationale and overcomplicated, overcentralized, and overbureaucratic system.

This is a personal opinion, of course.

The CHAIRMAN. Thank you, Mr. Field.

I think that is a good note on which to end these hearings for today.

Mr. SCHENCK. Mr. Chairman, also, if you mash the potatoes, you can put them in a smaller sack.

The CHAIRMAN. Mr. Cutler.

Mr. CUTLER. Mr. Chairman, on behalf of the pharmaceutical manufacturers, I would like to thank you and your colleagues on the committee for your patience that you have shown in permitting us to make such a full statement and the interest you have had in our views.

Thank you very much, sir.

The CHAIRMAN. Let me say on behalf of the committee to all of you who have appeared here in behalf of the pharmaceutical industry that we thank you for the contribution that you have made to this record.

We think that this has been a very profitable day and I hope the entire committee will be much better off with this record. The committee will adjourn until 10 o'clock in the morning.

(Whereupon, at 9 p.m., the committee recessed, to reconvene at 10 a.m., Tuesday, August 21, 1962.)

DRUG INDUSTRY ACT OF 1962

TUESDAY, AUGUST 21, 1962

HOUSE OF REPRESENTATIVES,
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE,
Washington, D.C.

The committee met, pursuant to recess, at 10:15 a.m., in room 1334, New House Office Building, Hon. Oren Harris (chairman of the committee) presiding.

The CHAIRMAN. The committee will come to order.

The first witness this morning will be Mr. James F. Hoge.

STATEMENT OF JAMES F. HOGE, ATTORNEY (ROGERS, HOGE & HILLS, ESQS.), ACCOMPANIED BY WILLIAM F. WEIGEL, ATTORNEY

Mr. HOGE. Mr. Chairman, may I have my partner to sit by me?

The CHAIRMAN. Yes.

I think you should identify him for the record, Mr. Hoge.

Mr. HOGE. Mr. Chairman, this is Mr. William F. Weigel, a partner in my firm of Rogers, Hoge & Hills in New York.

The CHAIRMAN. Very well, Mr. Weigel. We are glad to have you with the committee.

Mr. Hoge, you may proceed.

Mr. HOGE. Mr. Chairman and gentlemen of the committee, my name is James F. Hoge. I am a member of the bar of the State of North Carolina and of the State of New York. I am a native North Carolinian and practiced law in that State for about 8 years before going to New York in 1930. My address is 41 East 42d Street in the city of New York and I am engaged in the active practice of law as a member of the firm of Rogers, Hoge & Hills. I appear on behalf of the Proprietary Association, the address of which is 1717 Pennsylvania Avenue NW., Washington, D.C. I have been the general counsel of this association since 1934.

The association was organized in 1881 and has been in continuous existence since. Its active members—97 in number—are engaged in the manufacture and distribution of proprietary medicines—medicines which are completely compounded, packaged, and labeled for use by consumers. They are over-the-counter items not restricted by law or practice to prescription sale.

I would like to take a moment or two, Mr. Chairman, to say something about proprietary medicines. The term is one that is not readily defined. In fact, it is very difficult to find an authoritative definition of it.

The effect of the Durham-Humphrey amendment to the act, which was before this committee in 1951, an amendment to section 503(b)

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of the law, divided drugs into two classes. That was the effect of the amendment. One class is prescription drugs sold only on prescription, and the other class is over-the-counter drugs.

Now, the over-the-counter drugs really divide themselves into two classes: one, the so-called ethical; and the other, the one usually referred to as proprietary, although there is no exclusive on that term. The ethical over-the-counter drug is not necessarily prescribed, but it is advertised only through professional journals and circles, and the patient usually hears of it first from the doctor, either by prescription or by verbal direction to go get it.

It is with respect to the proprietaries, as they are usually called, those drugs which are advertised directly to the public which are not limited in any way to prescription sale. It is for that class which I appear.

I would like to go one step further with respect to proprietaries. So much of this legislation is applicable to the prescription drug. The drugs for which I appear perhaps do not rest upon the same high plane that a prescription drug does, but they are important, and I would like to read you just a line from a speech recently made by Dr. James F. Hundley, Assistant Surgeon General for Plans of the U.S. Public Health Service.

In May of this year he said:

> Remedies that are safe, effective, easily obtained, easily used and not easily abused are necessary and an important part of our scheme of total health care for the foreseeable future. Entirely aside from mental and physical benefit, such remedies prevent available health resources from being swamped by patients with real or imaginary symptoms which do not require skilled professional attention.

And one further word on that score, Mr. Chairman: These proprietary drugs went through a great transformation as a result of the 1938 law which was passed through this committee and by the Congress. As a result of that law, many so-called proprietary medicines came off the market. All of them underwent radical changes as to formula, labeling, and general distribution, so that this association for which I speak ardently supports the food and drug law. It ardently supports the administration of it, and it commends the Food and Drug Administration for the type of administration which this law has had at its hands over these years.

There are also 120 associate members in this association. They are companies which do not manufacture and distribute proprietary medicines but which are interested, as suppliers of various materials and services, in such manufacture and distribution.

The association must—at this time—be cast in opposition to this bill. But it is more agreeable to our sentiment, and closer to the fact, to say that we are for a revision of the bill. The association is not opposed to amending the law; is not opposed to keeping it up to date. The association and its members were very active during the 5 years that the present law was worked out in the Congress. The evolvement of the present law began with the bill introduced on June 12, 1933—S. 1944—generally referred to as the Tugwell bill. It was enacted on June 25, 1938, after numerous hearings and revisions in both Houses of the Congress.

It was before a subcommittee of this committee chaired by Mr. Chapman of Kentucky from June to September, 1935. From May 1935—when the bill passed the Senate—until the passage of the act

in June 1938, this association for which I speak was an active supporter of the legislation, and on August 10, 1935, I appeared before a subcommittee of this committee, Mr. Chapman's committee, already referred to, and stated the association's support of the bill which eventually became the law.

There were several bills before the subcommittee, some of which had been introduced here in the House, but the principal bill, and the one which, after revision, became law, was S. 5, which, of course, had been introduced in the Senate (74th Cong., 1st sess., H.R. 6906, H.R. 8805, H.R. 8941, and S. 5, pp. 694–698; S. 5 having passed the Senate on May 28, 1935).

SCOPE OF PROPOSED AMENDMENTS

H.R. 11581 proposes numerous amendments to the Federal Food, Drug, and Cosmetic Act—amendments which are extensive and complex. We think some are more extensive and complex than they need be, and it is to them that we direct our opposition and our request for revision. In their present form they would change the character of the law and, to a substantial degree, at least, replace a system of defined private responsibility with one of detailed governmental regulation, or license.

Some of the manufacturers of proprietaries have an interest in all of the drug provisions because they include affiliated companies or corporate divisions which manufacture prescription items. As to those, however, the Pharmaceutical Manufacturers Association has given particular study and made a full representation.

They were here, of course, yesterday with numerous witnesses. And I think I may, and I would like to say, Mr. Chairman, that this association associates itself with the position stated by Mr. Eugene Beesley in his statement yesterday in which he listed eight objectives or concepts of this bill with which his association is in agreement. And this association is in agreement with those concepts, too, and, like Mr. Beesley and his witnesses, our being here today is to ask revision in some of them and not to oppose the concept of improved food and drug legislation.

I shall, therefore, confine my statement—certainly in principal part—to the application of the bill to drugs which are made and sold for self-medication, the ones usually referred to as proprietary medicines.

SECTION 101, PAGES 2 AND 3, ADULTERATION, OR LICENSE?

The bill's first amendment applies to section 501 of the law. That is the section which defines adulteration of drugs. Under the amendment, section 501(a) would read as follows—the new matter being italicized:

"SEC. 501. ADULTERATED DRUGS AND DEVICES.—A drug or device shall be deemed to be adulterated—

"(a) (1) If it consists in whole or in part of any filthy, putrid, or decomposed substance; or (2) (4) if it has been prepared, packed, or held under insanitary

conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health; or (B)—

and this is the new part—

***if it is a drug and the methods used in, or the facilities or personnel or controls used for, its manufacture, processing, packing, or holding were inadequate (as determined in accordance with regulations promulgated by the Secretary on the basis of good manufacturing practice) (i) to insure that its identity and strength do not differ from, and that its purity, quality, and efficacy do not fall below, those which it purports or is represented to possess, or (ii) to insure that it will not be injurious to health when used in accordance with directions for use on its labeling, or when used in accordance with a prescription of a licensed practitioner (which prescription is consistent with its labeling), or (iii) to insure that its labeling is not such as to cause it to be adulterated or misbranded; * * ***

Since 1938 the law has provided that a drug shall be deemed to be adulterated if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth or whereby it may have been rendered injurious to health, and we have no objection to extending this to include inadequate methods, facilities, and controls.

Mr. Chairman, that language came into the law in 1933 to 1938 largely from the food provisions of the act. It was pointed out by numerous people that adulteration of a drug consisted really only in the change of its identity and quality and purity, but there were witnesses who suggested that these provisions about sanitary control from the food sections of the law might well be brought over to the drug provisions, and there was no objection to it. They were written into the law, and they have been there ever since, and we have no objection today to the amendment insofar as it adds methods, facilities, and controls.

However, the proposed amendment goes far beyond that and constitutes what is, in effect—in my view—licensing. On the manufacture, processing, packing, or holding of drugs, it would impose regulations—to be later made by the Secretary, and presumably to be changed from time to time, as he thinks they should be changed—as to facilities, personnel, methods, and controls. Often there is properly a choice between methods which may be used in making a given product. Manufacturers should have freedom of choice, as to which method they use, provided the end product meets the requirements of the law.

Facilities include machinery and other equipment, and often there may be different machines and equipment for making the same article. Here, too, manufacturers should have freedom of choice provided the end product is as it should be.

Our objection so far is to the Secretary doing this by regulation. But this amendment goes further. It even authorizes regulations whereby the Secretary would determine the adequacy of personnel employed by the manufacturer or processor. A proper judgment on the ability of individuals to perform their duties in the manufacture and processing of drugs should be, and usually is, based on close and long observation. It is a subjective judgment and cannot be made on arbitrary standardization. It is part of a manufacturer's right and responsibility to select personnel of character and ability.

The bill would rest these controls on a presumption. It would deem a drug to be adulterated if it does not comply with the Secretary's requirements as to methods, facilities, controls, and personnel. It need not—and may not—be actually adulterated at all. Personnel should not be included in the amendment. Methods, facilities, and controls should be, but the adequacy of them should not be left to administrative discretion as proposed.

The amendment goes on to deal with labeling. It proposes to control labeling—I suggest—by licensing. I think the effect of this section, as it is presently worded, is a matter of license, and under the fiction of adulteration.

Now, I use the word "fiction" not in any invidious sense at all. But to deem an article adulterated, if it is made under unsanitary conditions, or if it is made by inadequate machines and so on, I repeat, may not really affect the article; it may not adulterate it; but we create this legal fiction, and we say that it shall be deemed to be adulterated if it has been made by inadequate facilities, machinery, and the like.

The bill proposes at this point, therefore, to control labeling under this fiction of adulteration, and there is a prototype for it. It was in one of the early bills preceding the enactment of the 1938 statute. It was in S. 2800, which was introduced on February 6, 1934.

The Food and Drug Administration proposed in that bill—or perhaps I should say the bill proposed—that a drug should be "deemed" to be adulterated "if it is dangerous to health under the conditions of use prescribed in the labeling thereof".

It also appeared in S. 5, which, after revision, was passed by the Senate. Prior to passage by the Senate on May 28, 1935, the provision was taken out of the section on adulteration and put into the section on misbranding (S. 5, sec. 402(b)). As finally enacted into law, the provision appeared, as it does now, as section 502(j) and defines a drug as misbranded—

> if it is dangerous to health when used in the dosage or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof.

Mr. Chairman, may I say that that was heralded as a forward advance in the food and drug law. I remember so distinctly the advocacy of it. It was represented that here is a provision which will enable the Food and Drug Administration to apply an elastic test; that, after being specific about labeling and about adulteration and all of these matters, if the drug, as a matter of fact, is dangerous when it is used according to the directions on the labeling, then that drug is misbranded and subject to regulatory action.

It was, I say, heralded as a very forward advance in the making of food and drug laws.

The law presently has extensive provisions in section 502 for the control of labeling. That is the misbranding section of the act, and, in addition to 502(j) which I called the elastic provision, it has a great many specific, detailed regulations as to name and address, directions for use, warnings against use and other matter contained in that section.

The amendment in clauses (ii) and (iii), which I read to you a moment ago and which appears on page 4 of my statement which was handed up, seemingly is designed to "insure" (to use the word

of the amendment) that the labeling complies with section 502. In other words, where the act now imposes upon a manufacturer the duty to obey the requirements of section 502 of the law as to the correct labeling of his product, the amendment would impose upon him the duty to obey the regulations of the Secretary, would enforce that duty under the stigma and the penalty of "adulteration," and would be effective to make prior compliance with the Secretary's regulations a condition to the marketing of the article.

That is one of the reasons why I say this particular section is in effect licensing, because we are not waiting, as the present law does, to see what the manufacturer does. We are telling him in advance what he has got to do, and if he does not, his article will be adulterated and subject to the various sanctions—and to the stigma—of adulteration.

And there are drastic sanctions, among them seizure pursuant to libel (sec. 301 of the act). The law permits multiple or unlimited seizures as to adulteration. It limits seizures for misbranding to a single action except when the misbranding has been the basis of a prior judgment in favor of the United States or when there has been a finding of danger to health or when it is misleading in a material respect to the injury or damage of the purchaser.

Mr. Chairman, that was worked out in those years of 1933 to 1938, and this, briefly, was the idea. Misbranding is a matter of language. It may be serious or it may not be serious. It may be the matter of a misplaced word or the necessity for some further wording. In any event, and usually, it is something that can be corrected. It does not go to the inherent nature of the drug.

Therefore, the sanctions pertaining to it should be different from those pertaining to adulteration. Everyone back in those years was in favor of getting an adulterated drug off the market peremptorily, swiftly and without any limitation on the power of the Government to seize, but with respect to wording—misbranding, as we call it—you did write into the law at that time that there should be some limitation on the number of seizures which might be made in the first instance.

Now, this amendment would undo all of that. This amendment would carry us right back and would provide that a drug which is not branded according to the Secretary's directions, if you please, will be deemed to be adulterated and will be subject to multiple seizures and to all the other sanctions, criminal prosecution, injunction, and all.

With several notable and proper exceptions—and I emphasize the word "proper"—such as the new drug provisions, the existing law has not been one of license. The original design of it was to state, wherever possible, the duties of manufacturers and distributors and to empower the Food and Drug Administration to prosecute infractions of the law's requirements. Since enactment of the statute, there has been a tendency—justified by circumstances and acquiesced in reluctantly—to move away from that concept and toward one of licensing, to some extent. The new drug section did that. So did the food additives and color additives amendments, and the amendments with respect to antibiotics.

Now, I am not critical of those provisions of the law. I realize there must be exceptions to all rules, as we say, and that licensing at

times is proper and necessary. I am not critical. I am pointing out to you there has been this tendency; that the proposed legislation would accelerate that tendency and go far toward transforming the statute into one of Federal licensing.

Unless that is the purpose—and we do not believe that it is the purpose; I do not think it is the purpose of this committee, certainly—the bill should be revised on page 3, line 3, to read as follows. There would be the opening sentence:

> **A drug should be deemed to be adulterated—**
> **(B) If it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding are not adequate to assure that its identity and strength do not differ from and that its purity and quality do not fall below that which it purports or is represented to possess.**

What I have done in that suggestion is to delete the reference to personnel which appears in the amendment and to delete the clauses (ii) and (iii) at the end which refer to labeling and construe labeling as adulteration.

Then we come next to section 102, which appears at pages 3 and 4 of the bill, and has to do with efficacy, and I address myself at this point particularly to the amendment to section 201(p) of the existing law. That is the definition of "new drug" in the present law.

The amendment would amend that definition to include the words "efficacy" and "efficacious" in the definition of "new drug."

The definition presently relates only to "safety". The amendment would define a new drug as one which, to quote it in full:

> **is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety *and efficacy* of drugs, as safe *and efficacious* for use under the conditions prescribed, recommended, or suggested in the labeling thereof. [New matter italicized.]**

This amendment of the definition is, of course, related to amendments, later in the bill, which would add a determination of "efficacy" to the new drug controls in section 505 of the law. These amendments would be accomplished by the provisions appearing on pages 4 to 10, inclusive, of the bill. The basic change in section 505 would be to require affirmative approval or rejection by the Secretary of a new drug application and to condition approval on proof of efficacy as well as safety. These are important changes and have provoked considerable discussion.

But even if section 505 should be amended to make some provision for a showing as to efficacy as well as to safety, there is no need to amend the definition, and to do so may present serious trouble for proprietary medicines and particularly for those which have been on the market for many years—articles which have been generally recognized and considered to be safe but have not been through a new drug proceeding with respect to efficacy. The amendment of the definition is not necessary because—if efficacy is added to section 505—a new drug as presently defined (one which is not generally recognized as safe) will have to make the required showing on efficacy.

The only difference would be that under the present law, if you amend it to put efficacy in section 505, the machinery will not start until we pass the point of safety.

That is, any article which is not generally recognized as safe—and that is the present test, Mr. Chairman. The test is not that an article

is not safe: the test is that if an article is not "generally recognized as safe," then it must go through this proceeding, and if you amend 505, as has been proposed here, the Department would then go into questions of efficacy as well as safety.

The law now demands that the manufacturer of a proprietary drug make no claims beyond the efficacy of his product, but the amendment would prevent the marketing of the article until and unless the Secretary had approved the claims of its therapeutic worth. This could be very difficult for the manufacturer of an article to be used in self-medication. We must remember, as I just said, that the test proposed is that the article be—

recognized among experts qualified by scientific training and experience to evaluate the safety *and efficacy* of drugs, as safe *and efficacious* * * *.

Again, I am not critical of that language, but it is difficult language. It was difficult when it was worked out many years ago, and everybody knew it was difficult, but I suppose no one could think of anything better. There may be quite a big difference between a thing being actually safe and being generally recognized as safe. But the law has been these years that it is not generally recognized by experts.

Such experts, who in most instances, presumably, would be physicians, are sometimes loath to acknowledge articles for self-medication. They may concede—and they usually do as to the products of which I am speaking—the safety, or the harmlessness, of the article, but they frequently assert that the efficacy of medicines depends on the accuracy of diagnosis and the skill of the attending physician.

If the definition is to be amended as the bill proposes—our position is that the definition should not be so amended—then efficacy should not be included in the definition, and that was the position taken yesterday by the representatives of the Pharmaceutical Manufacturers Association. But, as a second line of defense, if you please, if the definition is to be amended as the bill proposes, then there should be an adequate grandfather clause. There is such a clause in the existing law, and there is the semblance of one in the bill. I call it semblance because I do not think it goes very far.

Section 108(c) (p. 15, line 20) provides that some of the amendments made by sec. 102 would not apply to articles on which there were effective new drug applications at the time of the enactment of the bill. But even there the clause is not applicable with respect to efficacy. It expressly excludes the amendment on efficacy, so that articles on the market prior to the enactment of the bill would be subject to new drug controls on efficacy.

Most proprietary medicines have not been subject to the new drug requirements and would become so now—if at all—solely because of the injection of the word "efficacy" in the definition. When the existing law was passed in 1938 it contained, as it still does, a grandfather clause. It is in section 201(p), which is the section defining a new drug, and provides that a drug—

shall not de deemed to be a "new drug" if at any time prior to the enactment of this Act—

the 1938 act—

it was subject to the Food and Drug Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use.

If the new drug definition is to be amended now to include efficacy, then the grandfather clause should be updated so as to cover drugs complying with the existing law at the time of the enactment of this bill. This could be accomplished by amending section 108(c) (p. 15, line 20) by inserting at the beginning of said subsection the following language:

The amendment made by section 102(a) of this Act to section 201(p) of the Federal Food, Drug, and Cosmetic Act shall not apply to any drug intended for use under conditions prescribed, recommended, or suggested in its labeling at the time of the enactment of this Act.

Mr. Chairman, that does nothing more than update the existing grandfather clause, and, insofar as I could, I adapted it to the exact language of the present law.

Now, under the present law and under the regulations pursuant to it, a drug may become a "new drug" if you change the formula or if you change the claims and the directions for use; that is to say, if such change in formula or directions breeds a question of safety, then an old drug would become a new drug for the purposes of the act.

So that is the reason for the language which I have suggested here: that as long as an article on the market, when this bill is enacted, has the same formula and the same directions and claims, then it will not be subject to the revised definition of "new drug," and that is precisely what the 1938 act did.

The manufacturers represented by the Pharmaceutical Manufacturers Association make the prescription drugs and are more closely concerned with the new drug provisions of the law than are the members of the Proprietary Association. Here, again, I would like to associate ourselves with the recommendations made by that association in the statements before this committee yesterday for amendments of the law.

While prescription drug manufacturers have in the past met the new drug provisions far more frequently than proprietary manufacturers, it would not be accurate to say that those provisions are unimportant to the proprietary people, and it is quite necessary to say that the proposed amendments may make the new drug provisions critically important to the proprietaries, and that is particularly so with respect to the definition.

PREVIOUS PROPOSALS ON "EFFICACY"

This is not the first time that a proposal to inject "efficacy" and "efficacious" has been before this committee. The Durham-Humphrey bill (H.R. 8289, 82d Cong., 1st sess.) proposed an amendment to section 503(b) of the law which would have provided that if the Administrator of the act—and it was then the Federal Security Administrator—found a drug—

to be unsafe or ineffective for use without the professional diagnosis or supervision of a practitioner licensed by law—

then the drug should be dispensed only on writteen prescription. The Senate bill (S. 1186, 82d Cong., 1st sess., in the nature of a substitute) provided for prescription dispensing of any drug which the Admin-

istrator determined "to be safe and efficacious for use" only under professional supervision, and he was authorized to make his finding—

on the basis of opinions generally held among experts qualified by scientific training and experience to evaluate the safety and efficacy of such drug.

There was much opposition to these provisions. On behalf of the Proprietary Association, I appeared before this committee and objected to such extension of the Government's authority (transcript of hearings, p. 194, May 3, 1951).

The reference to efficacy was stricken from the bill on the floor of the House on the motion of Representative Roberts of Alabama on August 1, 1951 (Congressional Record, p. 9544), who said:

Mr. Chairman, when this bill was being considered in committee there was quite a difference of opinion as to the meaning of the word "efficacy" and the meaning of the word "efficacious". Webster's dictionary defines efficacious to mean possessing the quality of being effective. Many of us feel perhaps that it is too broad, and, in fact, many of us voted to strike those words out of committee. I feel the bill will be just as good and will accomplish the same purpose and will answer some of the objections being made along the line that we are giving too much power to the Administrator.

The word "efficacy" came into the law with the amendment for batch testing of insulin and antibiotics (secs. 506 and 507). The law requires the testing of these articles for safety and efficacy of use. "Efficacy" in connection with those drugs relates to potency and, as I understand it, does not involve judgment as to therapeutic use.

In testifying recently before a subcommittee of the Judiciary Committee on the House on H.R. 6245, which is the companion bill to Senator Kefauver's Drug Industry Anti-Trust Act which was introduced by Mr. Celler, Commissioner Larrick was asked by Congressman Meader:

Just what was meant by efficacy, and just what authority is sought by the Food and Drug Administration with respect to efficacy? Is it only to determine whether or not the claims of the manufacturer as to efficacy are supported by evidence, or does it go beyond that and place the Food and Drug Administration in the position of determining therapeutic value in the absence of * * *?

Commissioner Larrick answered:

The sole purpose of our proposal is to place the burden of proof on the prospective manufacturer to show, in connection with his new drug application, that the drug will do what he claims it will do.

Mr. Meader asked:

And that is the limit?

Commissioner Larrick answered:

And it stops there.

Now, if that is the extent of the proposed amendment, it does not go beyond the substance of what the law now contemplates with respect to proprietary medicines. Procedurally—as to a new drug—it would shift the burden of proof. But if the labeling of a proprietary medicine today contains claims beyond what the medicine will do, it is misbranded and subject to the various, numerous, stated sanctions of the law. If the amendment means more than the Commissioner said it does, then the specter of licensing rises again.

PRIOR APPROVAL

The bill would amend the law to require "affirmative approval" of new drug applications (p. 7, line 8; p. 8, line 3). Under the law as it now stands, an application becomes effective on the 60th day after the filing (subject to postponements) unless the Secretary refuses "to permit the application to become effective." A requirement for affirmative approval could result in protracted delay in clearance, due to a predisposition against taking the responsibility for clearance, particularly in view of the unavoidable public inference that drugs approved by the Food and Drug Administration have been officially recommended. Affirmative approval was definitely and deliberately avoided in the development of the present statute.

That, of course, is not controlling upon us today, but it may be interesting. This new drug section got into the law under a sensational development. There was a drug down in Tennessee that combined sulfonilamide with, I think it was, diethylene glycol, as a solvent. It was an ethical drug; it was a prescription drug. There were some very unfortunate incidents, and the Congress was urged to adopt legislation to meet it, and the new drug section was worked out just prior to passage of the 1938 act.

I was present, and I remember the deliberations. It was no accident that the provision was put in this sort of negative or passive form, as it is, whereby a new drug application becomes effective if the Secretary does not reject it. The Food and Drug Administration in those days did not want the responsibility for affirmative approval; it did not want what amounted, virtually, to licensing.

Now, the Food and Drug Administration may have changed its mind by this time, and it has a perfect right to do so, but I thought I might say to you that it was not by accident that the law was put this way in the first place.

DOUBTS AND WITHDRAWAL

The bill (pp. 8 and 9) would also authorize the Secretary to withdraw this approval if it later appears to him that there is "substantial doubt" as to the drug's safety or efficacy—and it is largely the word "efficacy" that makes that phrase difficult. The bill would authorize suspension of the approval prior to hearing when the Secretary finds that there is imminent hazard to the public health. Appeal from the Secretary's order denying or withdrawing approval would go to the U.S. Court of Appeals rather than the District Court as is now the case.

With the injection of "efficacy" in the definition (sec. 201(p)), these amendments could affect over-the-counter medicines very seriously. These amendments would likely transform the present status of proprietary medicines (wherein the manufacturer has the responsibility for complying with the law) to a status of prior Federal licensing with consequent post-licensing controls.

SECTION 111, PAGE 17, ESTABLISHED NAMES

The bill, at this point, would create a new section to be identified as section 508. It would authorize the Secretary, by regulations, to specify a "standard name"—which would be the "established name"—for a drug whenever he considers is necessary or desirable in the interest of achieving usefulness or simplicity of drug nomenclature, or because there are two or more nonproprietary names for the same drug or for identical drugs, or because the "common or usual" name is not satisfactory.

Nomenclature in the present law includes "the name recognized in an official compendium" and the "common or usual name" (secs. 501(b), 502 (e) and (g)). The term "official compendium" means the U.S. Pharmacopeia, Homeopathic Pharmacopoeia, and National Formulary. There is, at present, no authority for the Secretary to specify the name of a drug to be used in an official compendium or elsewhere. The law requires that if a drug is not designated solely by a name recognized in an official compendium its label must bear the "common or usual name" of the drug, if such there be; and in case it consists of two or more ingredients, the "common or usual name" of each active ingredient.

As the section of the bill is worded, the Secretary's authority would apply to all drugs—prescriptions, over-the-counter, ethicals, proprietaries. It would also apply to "official" drugs, i.e., those listed in the compendia. The Secretary could establish names other than those by which drugs are there listed. With respect to proprietary products, most of them do not have "official" names. They are primarily unique preparations consisting of a combination of ingredients. Even where formulas are similar, the end products usually differ, sometimes substantially due to their excipients, binders, diluents, and dosage forms. It would be difficult and confusing to fix single established names for them. A very real objection arises upon the grant of this authority—unless the section is so amended as to limit it—in that the Secretary might determine the trademark associated with a drug to be its "established name." The bill, therefore, should contain a proviso against designation of trademarks as "established names."

Fear of the Secretary using such authority to appropriate trademarks is born of experience. In 1941 the Federal Security Administrator, who then enforced the act, proposed regulations under section 502(d) designating as habit-forming certain chemical derivatives of substances named in that section. The proposed regulation, as published in the Federal Register on January 30, 1941, page 680, stated:

> For the purposes of section 502(d) of the Federal Food, Drug and Cosmetic Act, each of the chemical derivatives hereinafter listed under its common or usual name, followed in certain cases by its chemical name, is hereby designated as habit-forming.

The proposed regulation listed numerous chemical derivatives of barbituric acid. At least 20 of the so-called common or usual names so listed were trademarks—many of them registered in the U.S. Patent Office. Pursuant to section 701 of the act, hearings were held from March 3 to March 12, 1941; 1,310 pages of testimony were transcribed. Briefs followed and thereafter the regulation was promulgated. It did not designate the trademarks as "common or usual names." It did,

however, list the trademarks as the "names" of the chemical derivatives.

Not until 1957 was there a correction. In 1957, the regulation was revised to list the substances in three parallel columns: First, the chemical description of the derivative; second, the "common or usual name"; and third, some "trade or other names." So it is now in this third column that trademarks properly appear (CFR title 21, sec. 165.1).

The bill makes no provision for hearings or appellate procedure with respect to the Secretary's designation of "established names." If this authority is to be vested in the Secretary, then in addition to there being a restraint against his designating trademarks as established names, there should be a provision that the designation should be subject to the provisions of section 701 of the act with respect to hearings and appeals.

May I just say that when this was attempted in 1941, there was not one word in the act to authorize the Secretary to designate the name of a product for any purpose. The Secretary could then, as he can now under the law, bring a proceeding in which he may charge that a trademark is in fact the common or descriptive name, and if he has the evidence and can prove his case he prevails. But there is not authority for him by regulations or otherwise to designate names for drugs.

SECTION 112, PAGES 18–20, ESTABLISHED NAMES VERSUS TRADEMARKS

This section of the bill is closely related to the preceding section. The importance of the authority to fix "established names" becomes clear here for section 112 would revise section 502(e) of the existing law to provide that a drug will be misbranded unless its label bears "the established name" (if such there be) and, in case the drug is fabricated from two or more ingredients, "the established name and quantity"—the words "and quantity" are brand new—"of each active ingredient." The "established name" of such drug or ingredient on the label and "on any labeling on which a name for such drug or ingredient is used" must be "given precedence in position over any proprietary name or designation for such drug or ingredient" and must be used "in type at least as large and prominent as that used for such proprietary name or designation."

Mr. Chairman, I think I should call your attention to the fact that the word "labeling" in this act has been construed by regulations and upheld by the courts to include all matter "accompanying" a drug. It doesn't have to travel in the same package or in the same freight car. If some matter for display on a druggist's counter arrives by some other means but it gets to the same place the drug does, it has been held that that material is "accompanying" or "accompanies" the drug and is thus labeling. I am not critical of that, Mr. Chairman. I simply am trying to explain the scope and extent of this amendment. And so to read the amendment on the label—and on the "labeling," meaning all of this other material—the "established name," as the bill calls it, would have to be given precedence over the trademark. I suppose that means that wherever the trademark appears it would have to yield precedence to the "established name," be it on a label or in context matter or what.